Energy Metabolism and Inflammation in Brain Aging and Alzheimer's Disease

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Abstract

The high energy demand of the brain renders it sensitive to changes in energy fuel supply and mitochondrial function. Deficits in glucose availability and mitochondrial function are well-known hallmarks of brain aging and are particularly accentuated in neurodegenerative disorders such as Alzheimer's disease. As important cellular sources of H_2O_2, mitochondrial dysfunction is usually associated with altered redox status. Bioenergetic deficits and chronic oxidative stress are both major contributors to cognitive decline associated with brain aging and Alzheimer's disease. Neuroinflammatory changes, including microglial activation and production of inflammatory cytokines, are observed in neurodegenerative diseases and normal aging. The bioenergetic hypothesis advocates for sequential events from metabolic deficits to propagation of neuronal dysfunction, to aging, and to neurodegeneration, while the inflammatory hypothesis supports microglia activation as the driving force for neuroinflammation. Nevertheless, growing evidence suggests that these diverse mechanisms have redox dysregulation as a common denominator and connector. An independent view of the mechanisms underlying brain aging and neurodegeneration is being replaced by one that entails multiple mechanisms coordinating and interacting with each other. This review focuses on the alterations in energy metabolism and inflammatory responses and their connection via redox regulation in normal brain aging and Alzheimer's disease. Interactions of these systems is reviewed based on basic research and clinical studies.

Keywords

Mitochondria; Glucose Metabolism; Redox Control; Inflammation; Brain aging; Alzheimer's disease

1. Introduction

The aging brain reveals a plethora of correlated processes that contribute to its senescence, yet to be fully understood on a molecular level. Age-related cognitive decline is one of the

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major risk factors for Alzheimer's disease (AD) and other prevalent neurodegenerative disorders [1]. Neurons are capable of surviving for more than a hundred years and staying functionally competent, but aging is their biggest adversary. Bioenergetic deficits, oxidized redox environment, and low-levels of chronic inflammation are major contributors to the cognitive decline associated with brain aging and neurodegenerative disorders like AD.

The brain utilizes ~25% of the total body glucose [2], and the majority of which is used to transduce energy through glycolysis and mitochondrial oxidative phosphorylation to support synaptic transmission. Aging induces changes in both glucose availability and the mitochondria energy-transducing capacity, including decline in neuronal glucose uptake, decrease of electron transport chain activity, and increase in oxidant production. Post-mortem tissues of AD patients exhibit disruptions of mitochondrial functions in the form of a dysfunctional tricarboxylic acid cycle (TCA), compromised electron transport and oxidative phosphorylation, as well as altered mitochondrial morphology [3]. The 'mitochondrial cascade hypothesis' proposes that in late-onset sporadic AD, the genetic makeup of a person's electron transport train sets the basis for oxidant production and the tone for oxidative damage, which drives the progression of other pathologies characteristic of AD [4].

Insulin and IGF-1 signaling (IIS) play critical roles in regulating and maintaining brain metabolic and cognitive function [5]. Preserved insulin sensitivity, low insulin levels, and a state of reduced flux through the IIS represent key metabolic features of a human longevity phenotype [6, 7]. Insulin signaling regulates mitochondrial function and its impairment causes abnormalities in mitochondrial function and biogenesis. On the other hand, controlled H_2O_2 production by mitochondria serves as a second messenger that enhances insulin sensitivity [8], while excessive levels of H_2O_2 activate stress-sensitive kinases (e.g. JNK and IKK), and lead to insulin resistance, and ultimately the bioenergetic deficits observed in the aging brain [9].

To add insult to injury, inflammatory processes are being associated with alterations in cellular metabolism [10, 11]. The activation of different types of brain immune cells such as microglia and astrocytes is one of the fundamental events in neuroinflammation [12]. Changes in the activation profile of microglia with age and increased release of inflammatory cytokines are hypothesized to induce development of insulin resistance [10, 11]. Amplification of the microglia-driven inflammatory responses by astrocytes generates neurotoxic factors leading to neurodegeneration [13]. A shift from a neurotrophic to neurotoxic phenotype in aging astrocytes thus denies neurons of essential energy substrates and neuro-protective mechanisms [14]. The activation of neuroinflammation is largely redox mediated, both at the molecular level in terms of redox sensitivity of key inflammatory components such as NFκB and inflammasomes, and at the cellular level where astrocytes transmit inflammatory signal to neurons via oxidants such as H_2O_2. The chronic inflammatory microenvironment, combined with a dysfunctional metabolic system is hypothesized to lead to neurodegeneration.

This review summarizes our current understanding of the relationship among metabolic, redox, and inflammatory changes in the brain as a function of age, and how these pathways

converge and contribute to physiological and pathological changes occurring in normal aging- and Alzheimer's brains.

2. Energy Metabolism in Brain Aging and Alzheimer's Disease

Neuronal glucose metabolism includes (1) mechanisms that control brain glucose uptake, such as insulin and the insulin signaling pathways (Fig. 1); (2) glucose transporter (GLUT)-dependent brain glucose uptake and the glycolytic pathway (Fig. 2), and (3) entry of glycolytic endpoints into mitochondria that are further metabolized in the TCA cycle and generate ATP through oxidative phosphorylation (Fig. 3). Because most of the neuronal energy-transducing pathways occur in mitochondria, it is important to consider that mitochondrial H_2O_2 participates in the regulation of redox-sensitive signaling, such as insulin/IGF1 (IIS) signaling, JNK signaling, and AMPK signaling. Mitochondria also receive and respond to cytosolic signaling, by which their metabolic and redox functions are modulated [15]. Overall, several signaling pathways and their second messengers, metabolites, transporters, receptors, and enzymes work in tandem with mitochondria to ensure adequate fuel supply and energy conservation to support neuronal function. As outlined in an earlier review [16], mitochondrion-centered hypometabolism is a key feature of brain aging and AD that is manifested by altered insulin signaling, decreased neuronal glucose uptake, changes in glucose receptors, and changes in the metabolic phenotype of astrocytes.

2.1. Insulin/IGF1 signaling (IIS) in brain aging and Alzheimer's disease

Insulin/insulin-like growth factor 1 signaling (IIS) is primarily orchestrated through insulin and IGF1, and the PI3K/Akt and ERK1/2 signaling pathways (Fig. 1). Following binding of the ligand to the insulin receptor, the activated signaling networks can be viewed in terms of critical nodes encompassed by the insulin receptor substrate (IRS), PI3K, and Akt [17]. Binding of PI3K to the phosphorylated IRS activates the PI3K/Akt signaling network, whereas recruitment of Grb2 to the IRS results in Sos-mediated activation of the Ras-MAPK pathway. The PI3K/Akt pathway effects changes in carbohydrate and lipid metabolism and modulates glucose uptake, whereas the Ras-MAPK pathway is involved in cell growth, cell differentiation and protein synthesis. Optimal IIS has been suggested to maximize life span and also control metabolic requirements for an energy-demanding organ such as brain [18]. The balance between of IIS- and JNK (c-Jun N-terminal kinase) signaling is crucial, for both elicit profound changes in mitochondrial function [19, 20]. Insulin resistance is usually accompanied by compromised mitochondrial function [21].

The physiological relevance of insulin in the brain has been increasingly recognized. The central nervous system was not considered to be an insulin-dependent tissue until the detection of insulin in brain [22]. In brain, the PI3K-Akt pathway is involved in glucose uptake, neuronal survival and synaptic plasticity [23, 24]. Conditional knockout of neuronal insulin receptors resulted in mice to be overweight, insulin resistant, and glucose intolerant [25].

IIS is also involved in the regulation of longevity. Early studies in *C. elegans* revealed that mutations of insulin receptor DAF-2 [26] or the PI3K AGE-1 [27] extended lifespan by

more than 100%. Later studies showed that mutation of the insulin receptor in adipose tissue was able to extend mouse lifespan by 18% [28]; similarly, brain-specific IRS2 knockout in mice led to ~18% extension of lifespan [29]. Conversely, insulin resistance is implicated in many adverse aging phenotypes and age-related conditions, which make the enhancement of insulin signaling also an anti-aging intervention. This paradox can perhaps be explained by the several orders of complexity in mammalian physiology and the recognition of insulin signaling being important in events beyond the regulation of carbohydrate and lipid metabolism. Moreover, genetic modifications to the entire IIS may have significantly different effects compared to insulin resistance, where only specific functions of the insulin pathway are impaired [23, 30]. It has also been suggested that each organism has an optimal level of IIS that maximizes lifespan and regulates metabolic requirements [18]. The notion of optimal IIS also seems consistent with the results showing regulation of lifespan by caloric restriction: progressive reductions in calorie intake promoted lifespan until the optimal IIS was reached, after which, additional reductions in calorie intake caused starvation and shortening of lifespan [31].

Brain aging is associated with a reduced IIS pathway entailing inactivation of the PI3K/Akt signaling in rats [32]. Interestingly, a high-fat diet that led to hepatic insulin resistance was able to induce impairment of the long-term potentiation (LTP) in the CA1 region of mouse hippocampi, which suggests the involvement of systemic insulin resistance in regulating brain bioenergetic and synaptic function [33].

Several studies pointed towards an impaired IIS pathway being involved in the pathogenesis of AD. Our study with a triple transgenic (3xTG) AD mouse model showed impairment of IIS associated with synaptic plasticity [34]. Diet-induced insulin resistance in a Tg2576 AD transgenic model promoted AD-type neuropathology [35]; intracerebroventricular streptozotocin injection to Tg2576 mice led to a brain insulin-resistant state, reduced spatial cognition, increased AD pathology, and increased mortality [36]. Intake of sucrose-sweetened water in APP/PS1 mice induced insulin resistance associated with memory impairment and Aβ accumulation in the brain [37].

In a clinical study, brain insulin resistance, IGF-1 resistance and IRS1 dysfunction, was shown to be early and common characteristics of AD [38]. Another clinical study observed severe deficiency of PI3K-Akt signaling branch of IIS accompanied by hyperphosphorylation of Tau protein in individuals with AD and type 2 diabetes mellitus [39]. A cross sectional population-based study found that features of insulin resistance were associated with AD, independent of the apolipoprotein E status [40]. A consequence from these clinical studies is the search for therapeutic options that alleviate insulin resistance and, thus, potentially halt AD progression [41].

2.2. Brain glucose uptake in brain aging and Alzheimer's disease

Studies examining brain glucose uptake have been mostly carried out using ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET), which allows measurement of glucose uptake but it does not represent the subsequent metabolism of glucose to CO_2. FDG, upon uptake to the cell, is phosphorylated to and trapped as FDG-6-PO_4, which emits a radioactive signal [42]. It is still not conclusive whether the majority of the brain glucose

enters astrocytes first via GLUT1 45kDa [43] or is transported directly from blood vessels to neurons via GLUT3 [44]. The exact modus operandi for the amount of direct glucose uptake into the neurons remains unclear and this perhaps, also raises some questions about FDG-PET data interpretation.

Aging is associated with an increased risk of deteriorating systemic control of glucose and of brain glucose uptake [45]. Several pre-clinical and clinical studies seem to support a role for lowered brain glucose uptake in age-associated cognitive impairment [43]. Dynamic micro-FDG-PET scanning showed lower brain glucose uptake in aged male Fischer 344 rats compared to younger controls [32], which is also seen in chronologically and reproductively aged female rats [46, 47].

FDG-PET in human subjects exhibited focal decreases in brain activity (particularly in the medial network) as a function of normal aging [48]. Declining brain glucose uptake was also accompanied by structural changes in the brain: (*a*) global thinning of cerebral cortex by middle ages was observed by high-resolution, structural MRI measurements in non-demented subjects [49]; (*b*) a significant age dependent decline of gray matter density and cortical matching algorithms was found over the dorsal, frontal, and parietal association cortices [50], and (*c*) cingulate sulcus enlargement was seen with age [51].

Although there are inconsistent studies about the status of brain glucose uptake during normal aging [43], there is overwhelming evidence about lower brain glucose uptake and metabolism being associated with AD [52]. Progressive decline of brain glucose uptake in AD and mild cognitive impairment (MCI) has been confirmed in multiple longitudinal studies. Cognitively healthy individuals with lower brain glucose uptake are more likely to be affected by MCI and/or AD dementia [53, 54]. Certain regions of the AD brain such as hippocampus, posterior cingulate, temporal, parietal, and frontal lobes have even more starkly lower brain glucose uptake [43]. Although decreased brain glucose uptake has been considered a predictor of progression to cognitive impairment or AD dementia, it still lacks enough information to allow the translation of those findings into a widely accepted diagnostic scan.

Brain glucose uptake can be separated into three steps (Fig. 2), (1) transport of glucose across the endothelium via GLUT1 (55kDa), (2) GLUT1 (45kDa) mediated transport of glucose into astrocytes, and (3) transfer of glucose into neurons via neuronal GLUTs [43]. A strong correlation has been established between decreased brain glucose uptake and decline in the expression of insulin-sensitive glucose transporters [29]. Fischer 344 rats showed decreased brain glucose uptake with age along with a parallel decrease in neuronal GLUTs. The expression of neuronal GLUT3 and GLUT4 decreased dramatically with age, whereas the expression of the vascular endothelium GLUT1 (55 kDa) decreased slightly with age [55]. Interestingly, the expression of the glia-expressed GLUT1 (45 kDa) increased with age; these results signaled towards a metabolic shift in neurons and astrocytes [32].

Similar to aging, AD is associated with decreased glucose transporter expression. In the APP/PS1 model, 18-month old mice had reduced GLUT1 expression in hippocampus compared to wildtype mice, whereas no difference were observed when they were 8 month-

old [56]. In male 3xTG-AD mice, there was a decline in the neuronal GLUT3 and GLUT4 [34]. In female 3xTG-AD mice, brain glucose uptake coincided with the decrease in the expression of GLUT3 but not GLUT4; this was also associated with a rise in inactive (phosphorylated) pyruvate dehydrogenase and in ketone body metabolism [57].

GLUT1 and GLUT3 levels in six brain regions of AD patients were reduced; the decreased GLUT3 levels in certain neurons compromised glucose availability and may be responsible for the deficits in glucose metabolism [58]. Studies on postmortem brains from AD patients revealed a decreased expression of GLUT1 and GLUT3, which correlated with abnormal tau hyperphosphorylation and downregulation of HIF1α (that leads to the transcriptional activation of GLUT); interestingly, GLUT2 expression was increased, likely due to astrocyte activation [59]. A large reduction (49.5%) of GLUT3 immunoreactivity was found in the dentate gyrus, a region whose cells are selectively destroyed in AD [60]. Reduced GLUTs expression in AD have also been found at the BBB and in the cerebral cortex [61].

2.3. Mitochondrial energy metabolism in brain aging and Alzheimer's disease

Mitochondria are at the center-stage of cellular energy supply and are particularly important for the brain because 90% of the glucose (primary source of brain energy) is oxidized to CO_2 in brain [62] (Fig. 3). The energy generated in this process is utilized to maintain neurotransmission and neuronal potential, and to prevent excitotoxicity [63]. Thus any alterations to neuronal glucose metabolism, largely supported by mitochondria, would affect neuronal function and ultimately affect cognition, learning, and memory.

The end metabolite of glycolysis, pyruvate, enters mitochondria via the mitochondrial pyruvate carrier (MPC) [64, 65] (Fig. 3). Pyruvate is the substrate for the pyruvate dehydrogenase complex (PDH); this is a central reaction in glucose metabolism and a decreased PDH flux was observed in rodent models of aging and AD [66]. The MPC acquires further significance when considering that decrease in its activity can lead to a reduced PDH flux. Acetyl-CoA, generated by the oxidative decarboxylation catalyzed by PDH, is then metabolized in the TCA cycle. Acetyl-CoA is also a co-substrate for the synthesis of N-acetylaspartate (NAA) by Asp-NAT; NAA is the most abundant amino molecule in the brain, considered a neuronal and axonal biomarker. Its breakdown product, acetate, functions in oligodendrocytes in the biosynthesis of myelin lipids [67]. Aspartate – generated by transamination from oxaloacetate– appears to be a limiting metabolite for proliferation when deficits in the electron-transport chain occur [68, 69]. α-ketoglutarate, an intermediate of the TCA cycle, is used for the conversion of glutamate and GABA, via glutamate dehydrogenase and glutamate decarboxylase (GAD), respectively [70] (Fig. 3). Reducing equivalents (NADH) from the TCA flow through the respiratory chain and the associated oxidative phosphorylation generates ATP. The latter along with glutamate and GABA are critical for the maintenance of synaptic plasticity.

Measuring glucose metabolism via ^{13}C-MRS/NMR involves supplying a ^{13}C-labeled glucose followed by measuring the glycolytic end product pyruvate and the downstream TCA cycle metabolites, neurotransmitters, and neurochemicals, such as glutamate, glutamine, GABA, and NAA [71, 72]. Metabolites generated from the labeled glucose have one or multiple ^{13}C in their structure based on how they were metabolized and the pattern

of ^{13}C labeling allows the determination of specific metabolism patterns. Thus, it is possible to follow the trail of glucose metabolism after glycolysis and estimate the amount of a specific metabolite (*e.g.,* glutamate) generated directly from the labeled glucose. Moreover, MRS/NMR methods employing ^{13}C-labeled substrates such as glucose and acetate allow direct assessment of neuronal and glial mitochondrial metabolism and facilitate distinguishing between them.

Mitochondrial brain glucose metabolism investigated in aged rats using [1-^{13}C]-glucose via ^{13}C and ^{1}H NMR spectroscopy revealed that the incorporation of glucose-derived ^{13}C into glutamate, glutamine, aspartate, and GABA declined in aged brain [73]. The SAMP8 mouse model of accelerated aging is characterized by spontaneous age-related learning and memory impairments associated with gliosis as a function of age [74]. SAMP8 mice, administered [1-^{13}C]-glucose and [1,2-^{13}C]-acetate, showed that major mitochondrial metabolites such as glutamate and glutamine derived from [1-^{13}C]-glucose and [1,2-^{13}C]-acetate were both significantly declined during aging [75].

^{13}C/^{1}H MRS studies in healthy brains showed that elderly subjects had ~30% lower neuronal mitochondrial metabolism (assessed by glutamate-glutamine cycle flux and TCA cycle flux) compared to young subjects [71, 76].. Interestingly, the astroglial rate of TCA cycle was ~30% higher in elderly group compared to young subjects, thus suggesting that normal aging was associated with a decline in neuronal metabolism along with an increase in glial metabolism as seen in astrocytes isolated from aged rats [14].

There are several studies on mitochondrion-driven glucose metabolism (measured by MRS/NMR) in rodent models of AD. Tg2576 mice showed a decrease in NAA, glutamate, and glutathione in the cerebral cortex at 19 months of age, which coincided with widespread AD-type pathology [77]. ^{1}H-[^{13}C]-NMR spectroscopy analyses of the APP_swe-PS1dE9 mouse model of AD showed a decrease in glutamate, GABA, and glutamine, which suggested an impaired glutamatergic and GABAergic glucose oxidation and neurotransmitter cycle in these mouse brains [78]. [1]H-^{13}C spectroscopy analyses of Thy-1-APPSL model, expressing mutant human APP, suggested that mitochondrial dysfunction may contributed to the glutamine synthetase impairment and increased metabolism of glutamate via the GABA shunt [79]. Glucose metabolism was clearly reduced by ~50% in a 3xTG-AD model as exhibited by the decreased levels of metabolites derived from the TCA cycle (glutamate, glutamine, GABA, and NAA) [80]. Clinically, a pilot study in AD patients receiving [1-^{13}C]-glucose probed for glucose metabolism using quantitative ^{1}H and proton-decoupled ^{13}C MR brain spectra, showed reduced glutamate neurotransmission which might contribute to cognitive impairment [81]. Interestingly, a hypermetabolic state was observed in younger triple transgenic mouse model of AD (7 months) in contrast to the hypometabolic state found in those mice that at older age (13 months). Hypermetabolism in the young AD mice was illustrated by prominent increases in ^{13}C labeling and enrichment of metabolites (e.g. glutamate and glutamine), glycolytic activity, TCA cycle activity, and glucose cycling ratios [82]. Consistently, ^{1}H and ^{13}C NMR spectroscopy analyses after infusion of [1-^{13}C]glucose and astrocytic substrate, [1,2-^{13}C]-acetate on P310L Tau transgenic mice revealed a hypermetabolic state in both astrocytes and glutamatergic and GABAergic cortical neurons [83].

TCA cycle also generates the NADH that flow through the respiratory chain, tightly coupled to oxidative phosphorylation. Deficits in the mitochondrial catalytic machinery (i.e., expression and activity of the respiratory chain complexes) along with an increase in the mtDNA mutations contribute to a hypometabolic state [84, 85]. Brains of rhesus monkeys had significant reductions in complex I and complex IV activities (with correction for the variable of mitochondrial enrichment) in an age-dependent manner [86]. The activity of complex I is 30% lower in the older rat brain mitochondria compared to young animals [87].

Brain mitochondria isolated from the Thy-1 APP mouse model of AD showed a reduced COX IV activity, mitochondrial membrane potential, and ATP levels at 3 month-of-age (accompanied with increased intracellular but not extracellular Aβ). Moreover, non-TG mice treated with extracellular Aβ showed significant decline in active respiration (state 3) and maximum respiration [88]. In the 3xTG-AD model, female mice showed a decreased expression and activity of complex IV coupled with compromised oxidative phosphorylation [89]. The impairments of mitochondrial complexes were also seen in clinical studies [3, 90]: a proteomic study in AD patients found that complex III core protein-1 in the temporal cortex and the complex V β-chain in the frontal cortex were significantly reduced [91]. In another study, mitochondria from AD patients exhibited suppressed activity in all respiratory chain complexes with a dramatic decline in complex IV activity [92, 93]. Compromised mitochondrial function in AD was also related to direct effect of Aβ on mitochondrial OXPHOS. Mitochondria localized Aβ levels negatively correlated with mitochondrial respiratory function, and with cognition [94], which is consistent with another study in which Aβ was found to inhibit mitochondrial complexes I and IV activity [95].

3. Mitochondrial Redox Control in Brain Aging and Alzheimer's Disease

Mitochondria are effective sources of H_2O_2, which accounts for changes in the cellular redox environment that characterizes brain aging. Oxidized redox status is a feature of AD [96, 97].

Mitochondrial H_2O_2 originates from dismutation of $O_2^{\cdot-}$, the formation of which is accounted for by different mechanisms [98–101]. While uncontrolled production of H_2O_2 overwhelms the reducing capacity of the cell, regulated H_2O_2 participates in the redox regulation of cytosolic signaling and nuclear transcription pathways [102].

3.1. Mitochondrial H_2O_2 and redox signaling

Mitochondrial H_2O_2 participates in the regulation of multiple cytosolic signaling pathways such as the IIS and the MAPK signaling. In neurons and hepatocytes, mitochondrion-generated H_2O_2 is found to activate IIS [103]. Low levels of H_2O_2 generated by mitochondria are actually required for the initial activation of IIS and this process is termed as "redox priming". Collapse of the neuronal mitochondrial proton gradient by FCCP not only eliminates mitochondrial O_2 consumption and H_2O_2 production, but also suppresses the phosphorylation (activation) of the insulin receptor even in the presence of insulin [103]. This is consistent with the observation that the spike signal of mitochondrion-generated H_2O_2 precedes the autophosphorylation of the insulin receptor, and that phosphorylation can be dose-dependently inhibited by N-acetylcysteine [104]. IIS is sensitive to H_2O_2 due to: (*a*)

the oxidation of cysteine residues on the insulin receptor and IGF-1 receptor facilitates autophosphorylation of both receptors and leads to the activation of the downstream IRS [105] and (*b*) H_2O_2 oxidizes and inhibits two negative regulators of IIS – the tyrosine phosphatases (*e.g.,* PTP1B) and the lipid phosphatase (PTEN) [106]. Moreover, mitochondrial H_2O_2 is also involved in the activation of Akt and its translocation to mitochondria and to the nucleus [107]. Nevertheless, increasing evidence suggests that H_2O_2 modulates IIS in a concentration-dependent manner (Fig. 4): while lower concentrations of H_2O_2 (~5 μM) activate IIS, higher levels (~50 μM) inactivate IIS [108]. IIS inactivation is likely due to the stimulation by elevated H_2O_2 of inhibitory pathways of IIS such as JNK and IκB kinase (IKK) [19, 20], which constitutes the mechanism of stress and inflammation-induced insulin resistance, respectively [109]. The activation of JNK by H_2O_2 has been thoroughly investigated [110–113] and it occurs at several levels: (a) H_2O_2 oxidizes thioredoxin and releases the upstream kinase of JNK, ASK1 [114], (b) H_2O_2 oxidizes and inhibits MAPK phosphatases [115], and (c) H_2O_2 disrupts the glutathione transferase-JNK complex and releases the latter [116]. IIS activity (IRS1 and Akt activation) declines in both the aged rat brain and 3xTG-AD mouse brain, whereas JNK phosphorylation and activity is increased in both models with aging or with AD genotype [32, 34]. Moreover, a recent study in the same 3xTG-AD model indicates that biliverdin reductase-A (BVR-A) is also connecting oxidative changes to insulin resistance via the inactivation of BVR-A and mTOR hyperactivation [117], which is consistent with clinical data from MCI and AD subjects [118].

3.2. The Mitochondrial Redox System

Maintenance of the mitochondrial redox status is determined by the balance between the sources of H_2O_2 and its reduction to H_2O by the glutathione peroxidase (GPx)-GSH and thioredoxin-2 (Trx2)-peroxiredoxins systems.

GSH-supported system—GSH synthesized in cytosol enters mitochondria and provides reducing equivalents to GPxs for H_2O_2 removal [119]. GPx1 localized in the matrix and GPx4 in the inter-membrane space are the two major GPx isoforms associated with mitochondria. While GPx1 is primarily involved in reducing H_2O_2 in mitochondrial matrix, GPx4 in both the cytosol and the mitochondria is vital to protect the cell from lipid hyperoxidation [120, 121]. GSH is regenerated from GSSG by glutathione reductase using reducing equivalents from NADPH. Mitochondrial GSH levels positively correlate with cellular viability [122, 123]. In both neurons and astrocytes, depletion of mitochondrial GSH leads to an increase in H_2O_2, loss of mitochondrial membrane potential, as well as cell death [124, 125]. Reagents that increase mitochondria GSH levels protect neurons against oxidant-induced neurotoxicity [126]. During aging, oxidation of mitochondrial GSH to GSSG [127, 128] is accompanied by mitochondrial DNA (mtDNA) oxidation in rodents [129, 130]. A clinical study to noninvasively quantify GSH in the occipital cortex of healthy young and old human subjects suggests that the old group has ~30% lower GSH levels than the young group [131]. The age-dependent decline in GSH levels in brain has also been connected with impaired cognitive function in aging. Treatment of rodents with compounds that acutely deplete GSH in the brain results in deficits in short-term spacing memory as well as impairment of LTP [132, 133].

Trx-supported peroxiredoxin system—In this system, electrons are transmitted from NADPH to Trx2 by thioredoxin reductase 2 (TrxR2) and eventually to H_2O_2 via peroxiredoxins [134]. Prx3 and Prx5 are the two mitochondrial Prxs that reduce H_2O_2, organic hydroperoxides, and peroxynitrite (ONOO$^-$) [135]. Prx3 catalyzes the removal of up to 90% of mitochondrial H_2O_2 especially at low H_2O_2 levels due to its high reaction rate constant (10^7 M^{-1}s^{-1}) [136]. Real time monitoring indicates that the removal of H_2O_2 in brain mitochondria is primarily a function of the Trx/Prx system with the GSH/GPx system contribute a small percentage [137]. Interestingly, high concentrations of H_2O_2 suppresses the peroxidase activity of Prx3 by hyperoxidizing it to the sulfinic acid form (Prx3-Cys-SO$_2$H) [138], which can be converted back to the sulfenic acid form (Prx3-Cys-SOH) through an ATP-dependent reaction catalyzed by sulfiredoxin (Srx) translocated into mitochondria [139, 140]. During aging, the inactivated, hyperoxidized Prx3 accumulates in liver mitochondria, with the reduced form remains the same as that of young rats [141]. This study confirms the increased H_2O_2 production and oxidized redox status in aged mitochondria. The imbalance between reduced and hyperoxidized Prx3 that occurred with aging could be ascribed to a decreased Srx activity in mitochondria and to the decline in mitochondrial protease activity involving the matrix-localized, ATP-stimulated Lon protease [142].

In the brain, Prx3 protects neurons against excitotoxicity while it suppresses astrocyte proliferation in specific brain regions [143]. Prx3 was also found to be involved in various neurodegenerative disorders such as AD, Parkinson's disease, amyotrophic lateral sclerosis, and Down syndrome [144]. AD patients exhibit a significantly lower expression of Prx3 in the brain than the normal subjects [145]. In AD mouse models, Prx3 overexpression protects both the APP transgenic- or non-transgenic mice from mitochondrial dysfunction and cognitive decline [146]. Prx3 transgenic mice exhibited enhanced mitochondrial function coupled with reduced oxidative stress compared with control group; relative to the APP single transgenic mice, APP+Prx3 double transgenic mice exhibited enhanced mitochondrial function, improved cognition, and reduced brain Aβ loading [146].

Prx5 is a 17 kDa atypical 2-Cys Prx [147]. In addition to mitochondria, Prx5 occurs in other intracellular compartments such as peroxisome, cytosol, and nucleus. Prx5 has a higher reaction rate with peroxynitrite and alkyl hydroperoxides than that with H_2O_2 and, unlike Prx3, it is insensitive to H_2O_2 hyperoxidation [148]. Prx5-deficient cells have increased oxidative macromolecule damage and are more susceptible to cell death [149, 150]. Conversely, overexpressing Prx5 in CHO cells protects mtDNA from H_2O_2 induced oxidation [151].

In addition to being a H_2O_2 scavenger, oxidized Prx1 and Prx2 could act as a H_2O_2 signal receptor and transduce signals to redox-sensitive target proteins [152, 153]. By forming a transient mixed disulfide intermediate with a nearby target protein, H_2O_2-oxidized Prx transmits redox signals from H_2O_2 to that target protein. The target protein, rather than Prx itself, is later reduced by Trx [152, 153]. These studies suggest a new paradigm in redox signaling that allows the spatiotemporally precise regulation of redox-sensitive proteins especially those that have a low intrinsic reactivity with H_2O_2, such as some transcription

factors and kinases. It is still to be determined whether mitochondrial Prxs are involved in this redox relay to facilitate H_2O_2 oxidation of mitochondrial proteins.

The intermolecular disulfide formed upon H_2O_2-driven oxidation of the two cysteine residues of Prx3 is reduced back by Trx2 in mitochondria [154]. Trx2 is abundantly expressed in mitochondria of tissues with high metabolic rate [155]. Trx2 is involved in apoptosis by interacting with the mitochondrion-localized apoptosis signal-regulating kinase 1 (ASK1). When Trx2 is oxidized by inflammatory or oxidative stimuli, ASK1 disassociates from Trx2 and phosphorylates downstream pro-apoptotic kinases such as p38 and JNK [156]. Interestingly, the Trx system is also implicated in the long-living Ames dwarf mouse. In these growth hormone (GH)-deficient mice, the expression and activity of both Trx2 and thioredoxin reductase-2 (TrxR2) are higher than those in the wild type mice. Such an upregulation of Trx2 system in these long-living mice is reversed by a 7-day treatment of GH [157], suggesting the correlation among reduced GH signaling, enhanced oxidative stress resistance, and extended life span. The expression of Trx2 in hippocampi of AD brains is significantly lower than that in control brains [158].

The expression of TrxR2, that catalyzes the NADPH-dependent reduction of oxidized Trx2, decreases with age in multiple tissues [159]. TrxR2, together with NADPH supply, could be key aspects that account for the dysregulated redox status during aging and neurodegeneration [160].

3.3. Interconnected mitochondrial energy- and redox systems

Both the GSH and Trx systems in mitochondria use NADPH as the ultimate reducing equivalent through glutathione reductase and TrxR, respectively. Sources of NADPH in mitochondria are the activities of nicotinamide nucleotide transhydrogenase (NNT), isocitrate dehydrogenase 2 (IDH2), and malic enzyme, with the NNT accounting for ~50% of the total NADPH production [161].

Under physiological conditions, NNT catalyzes the reduction of $NADP^+$ to NADPH using electrons from NADH and proton gradient force built on the mitochondrial inner membrane [162]. The mitochondrial energy-transducing component is thus connected with the mitochondrial redox system by NNT, given that the NADH is primarily generated in TCA cycle, and that the proton gradient is built by the electron transport chain. Oxidative challenges by cigarette smoke, which contains high amount of oxidants and electrophiles, upregulates NNT expression [163]. Silencing of NNT in PC12 cells leads to lowered ratios of $NADPH/NADP^+$ and GSH/GSSG, elevated H_2O_2 production, and compromised mitochondrial metabolic capacity. NNT suppression also induces accumulation of oxidized mitochondrial Prx3 [164], as well as the activation of intrinsic apoptosis through the activation of redox-sensitive JNK pathway [112]. The activity of NNT in male Fischer 344 rats declines as a function of age in 6-, 14-, and 26 month-old rats (Yin et al., unpublished data). NNT expression in mouse brain also declines during aging from middle age (11 month) to old (21 month) and its expression is lower in brains of the 3xTG-AD mice at both 11- and 21-month, compared to age-matched non-TG controls [165].

Under some pathological conditions, NNT in heart catalyzed the reverse reaction to generate NADH using reducing power from NADPH [166]. Upon increased metabolic demand, NNT switches to the reverse mode and consumes NADPH for NADH production, which impairs the capacity of mitochondrial redox systems to remove H_2O_2 and ultimately results in oxidative stress and cell death [166]. The activation mechanism of NNT reverse mode requires further investigation as well as involvement of this mechanism in tissues other than the heart, such as the brain.

Mitochondrial energy status determines redox capacity via NADPH-generating enzymes such as NNT and IDH2. On the other side, perturbations of the mitochondrial redox status alter the bioenergetic function via oxidative- or nitrosative post-translational modifications of key metabolic enzymes, including aconitase [167], α-ketoglutarate dehydrogenase [168], malate dehydrogenase (MDH) [169], succinyl-CoA-3-oxaloacid CoA transferase (SCOT) [170, 171] and complexes I [172], II [173], and V [170, 171] (for detailed review, see [15]). While oxidative modifications of these enzymes mostly lead to the inhibition of their activity in MCI or AD, the activity of MDH was found to be increased in MCI [174, 175]. Moreover, cytosolic redox status affects the utilization of different fuel substrates for energy transducing within the mitochondria by modulating cytosolic glycolysis and pentose phosphate pathway (PPP) [176, 177]. In lung cells, oxidative reagents such as cigarette smoke or acrolein suppress glycolysis and glucose-dependent ATP production by oxidizing and inhibiting the glycolytic enzyme, glyceraldehyde 3-phosphate dehydrogenase (GAPDH). This suppression of glycolysis reroutes glucose to the PPP to generate more NADPH to combat oxidative challenges [176, 177]. Due to the limited pyruvate transport into mitochondria, fatty acid transporters including carnitine palmitoyltransferase 1 (CPT1) and cluster of differentiation 36 (CD36) are upregulated, thus enhancing the utilization of fatty acids as fuel substrates. This shift in energy substrates reduces fatty acid supply to the surfactant biosynthesis and is thus implicated in the progression of chronic obstructive pulmonary disease (COPD) [176, 177]. These studies extend the inter-regulations between the mitochondrial energy and redox pathways to their cytosolic counterparts.

4. Inflammatory Responses in Brain Aging and Alzheimer's Disease

The immune privilege of the CNS prevents circulating immune cells from gaining access to it without the occurrence of inflammation or injury [178]. While a prolonged inflammatory state in the brain is detrimental to its function, the brain innate immune system can also be beneficial, since it promotes cellular repair and clears debris.

4.1. Brain cell types involved in neuroinflammation

Microglia is the major effector of the innate immune system and are ubiquitously distributed in the brain. Microglia use highly motile processes to survey nearby regions for the presence of pathogens and cellular debris, while synthesizing factors important for tissue maintenance. Microglia also help maintain plasticity of the neuronal circuits, and contribute to the protection and remodeling of synapses. These functions of microglia are partly mediated by the release of trophic factors, such as brain-derived neurotrophic factor (BDNF), which is important for memory formation and learning. Upon activation by

pathological triggers, microglia migrate to the site of injury, where they initiate an immune response. Changes in the function or activity of microglia, as a result of aging or neurodegeneration, may contribute to pathology progression. Along with microglia, astrocytes and endothelial cells also express innate immune receptors and contribute to inflammatory responses in the brain [179]. While astrocytes are mainly involved in maintaining neuronal function, they are also known to mediate neuroinflammation by receiving and amplifying inflammatory signals from microglia, and form the self-propagating cytokine cycle which generates large amounts of cytokines and oxidative signals [180].

4.2. Molecular components in inflammatory response

An inflammatory response typically involves three stages: TLR-NFκB formation of procytokines, inflammasome assembly, and activation of caspase-1. The detection of pathological triggers in an inflammatory response is mediated by pattern recognition receptor (PRRs) such as TLRs that recognize danger-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs). The downstream signaling pathways affected regulate the activities of transcription factors NFκB and AP-1, which induces the expression of effector proteins, such as components of the inflammasome (e.g., NLRP3, NLRP1, NLRC4), cytokines, oxidants and NO.

NFκB signaling—NFκB regulates immune responses through the transcriptional regulation of cytokines and immune response genes [181]. Under basal conditions, In response to stimuli-induced phosphorylation of IκB, NFκB dissociates from the complex and translocates from cytosol to the nucleus to induce the transcription of its target genes [182] (Fig. 5). NFκB is sensitive to redox changes and inflammatory mediators and participates both protective and damaging responses, based on the context of stimulation. H_2O_2 can positively or negatively modulate NFκB activity. Mitochondria-derived H_2O_2 is key to the activation of NFκB [20, 183]. Although excessive levels of H_2O_2 inactivate NFκB through oxidation of its p50 subunit, moderate levels of H_2O_2 lead to IKK- or Syk-induced phosphorylation, polyubiquitination, and degradation of IκB, and the activation of NFκB [184, 185] (Fig. 5). NFκB can have a pro-survival role by inhibiting JNK, upregulating anti-apoptotic genes, and decreasing the expression of manganese superoxide dismutase (MnSOD). Conversely, NFκB activation can be damaging to cells by initiating and amplifying inflammatory gene expression [186–188]. NFκB and MAPK pathway activation is apparent in oxidative stress and Aβ-induced neuronal cell death [189–191]. Interestingly, the outcomes of NFκB activation can be age-dependent: its activation by TNFα is neuroprotective against excitotoxicity and ischemic brain injury in 10 month-old neurons, but the same stimulus in 24 month old neurons was shown to be toxic [192].

Inflammasomes—Cellular insults identified by PRRs activate cytosolic multiprotein complexes called inflammasomes, which are responsible for the maturation and release of pro-inflammatory cytokines and the activation of pyroptosis, an inflammatory form of cell death [193]. The inflammasomes are either members of the NLR family or members of the pyrin and HIN domain-containing (PYHIN) family [194]. A total of 23 genes encode the NLRs, but only a few are capable of forming oligomeric complexes that activate caspase-1

[195], including NLRP1, NLRP2, NLRP3, NLRP6, NLRP12 and NLRC4 [196, 197]. The activation of most inflammasomes requires a priming stimulus (signal 1) and an activating stimulus (signal 2). Inflammasome complexes are generally composed of three components: a cytosolic PRR, caspase-1, and an adaptor protein, ASC (apoptosis-associated speck-like protein containing a caspase activation and recruitment domain). A priming stimulus, through activation of NFκB signaling, often leads to assembly of the inflammasome complex, which increases expression of prointerleukin-1β (pro-IL1β) and the inflammasome (*e.g.,* NLRP3). Activated inflammasomes oligomerize to form a platform with ASC that can activate caspase-1 (Fig. 6). ASC facilitates interaction between the PYD domain of the NLRP proteins and the CARD of procaspase-1. Caspase-1 regulates the maturation and release of IL-1β and IL-18 and also triggers pyroptosis pathways [194].

NLRP3 inflammasome is the most widely studied member of the NLR family. It can be activated by a wide array of stimuli, including APMPs such as bacterial, fungal and viral components, as well as DAMPs such as extracellular ATP, and it can also be stimulated by H_2O_2 and amyloid-β in the brain. Its ability to respond to a wide variety of stimuli suggests that it behaves as a general sensor of cellular damage and stress. The activity of NLRP3 seems crucial in the pathogenesis of different degenerative disorders such as AD, atherosclerosis, liver cirrhosis, and lung fibrosis [194].

The exact activation mechanism of the NLRP3 inflammasome is under debate, but all the proposed models postulate that cytoplasmic K^+ concentration plays a crucial role. Three models have been proposed. *(a)* The channel model proposes extracellular ATP to be the main activator, which activates the P2X7 K^+ release channel, which ultimately gives rise to pannexin 1 pore formation. The pores (which can be formed by bacterial toxins as well) allow cytoplasmic entry of extracellular factors that directly activate NLRP3 and also allow K^+ efflux out of the cell [198, 199]. *(b)* The lysosome rupture model fits when the activating stimuli are particulate activators (*e.g.,* alum and silica). It proposes that these particles are phagocytosed, causing lysosomal rupture release of Cathepsin B into the cytoplasm, which activates the NLRP3 inflammasome [200, 201]. *(c)* The H_2O_2 model, being the most relevant model in the context of this review, proposes NLRP3 to be a general sensor of cellular stress, where H_2O_2 serves as the secondary messenger that activates the inflammasome [202, 203] (Fig. 6)., and it will be particularly discussed.

4.3. Redox regulation of NLRP3 inflammasome

All NLRP3 activators have been found to be able to trigger oxidant production, whereas treatment with antioxidants blocks NLRP3 activation [204]. H_2O_2-triggered binding of NLRP3 to Trx-interacting protein (TXNIP), production is proposed to be the mechanism underlying the redox activation of NLRP3 [202]. Under resting mode, TXNIP is bound to Trx [205] and increased cellular H_2O_2 production dissociates this complex, thereby allowing TXNIP to bind to NLRP3, thus and leading to the activation of the latter (Fig. 6). Knockdown of Trx potentiated inflammasome activation and knockdown of TXNIP inhibited activation of caspase-1 and IL1β secretion upon stimulation by NLRP3 agonists [202, 206]. However, caspase-1 activation is not completely blocked when TXNIP is knocked out, suggesting that there are multiple pathways being capable of activating

NLRP3. Redox changes are also important in priming of the NLRP3 inflammasome. Priming of the inflammasome, which involves the TLR/NFκB signaling, can occur through its deubiquitination in the presence of mitochondrial H_2O_2 [195]. Several questions about the oxidant-dependent model of NLRP3 activation remain unresolved, and not all the stimuli that lead to oxidant production were able to activate NLRP3 (*e.g.,* TNFα). This implies that activation of NLRP3 follows a specific mechanistic pathway, in which oxidants or specifically H_2O_2 are essential but are not sufficient. In addition, in contrast to the H_2O_2 model of NLRP3 activation, $O_2^{\cdot-}$ was found to inhibit caspase-1 activation via redox signaling [207].

NADPH oxidases (NOX) were initially thought to be the primary activators of the NLRP3 inflammasome via the production of $O_2^{\cdot-}$ and H_2O_2. Some early inflammasome studies reported the NOX enzymes to be important in activating NLRP3 in response to ATP and particulates [206, 208]. However, macrophages deficient in certain NOX subunits, like NOX1, NOX2, NOX3, and NOX4, responded normally to activating stimuli, and in some cases, demonstrated slightly increased inflammasome activity, suggesting either compensation by remaining members of the NOX family or occurrence of a other cellular sources of oxidants for inflammasome activation [209]. In the CNS, NOX function is required for proper neuronal signaling and cognitive function, but overproduction of superoxide radicals contributes to neurotoxicity and neurodegeneration [210]. Increased activation of microglial NOX enzymes was found in the brains of AD patients [211]. However, in normal aging mouse brains, NOX activity was only upregulated in the 24-month-old mice when challenged by a high fat diet [212], suggesting age-related increase in sensitivity to activating stimuli in the brain.

Recent studies suggest that mitochondria might be the organelles that integrate signaling for inflammasome activation [209]. There is also evidence showing that NOX activation (and the generation of $O_2^{\cdot-}$ and H_2O_2) requires initial priming by mitochondrial H_2O_2 [213]. In non-stimulated conditions, the NLRP3 protein is localized at the endoplasmic reticulum (ER) but not mitochondria. This localization changed upon activation of the inflammasome in response to several different stimuli: NLRP3 translocated to the perinuclear space, where it also co-localized with ER and mitochondria. A similar ER/mitochondrial co-localization was observed for ASC upon NLRP3 activation, and TXNIP was found to redistribute to the mitochondria upon inflammasome activation. Depletion of mitochondrial DNA or inactivation of the voltage dependent ion channel (VDAC) was shown to impair inflammasome activation. VDAC proteins, abundant in the outer mitochondrial membrane, are channels responsible for ions and metabolite exchange between mitochondria and the rest of the cell, particularly the ER. They are also involved in the regulation of mitochondrial metabolism and mitochondrial $O_2^{\cdot-}$ release [214], and their nitration is significantly increased, indicative of changes in redox homeostasis, in AD brains [215]. Additionally, inhibition of mitophagy/autophagy by 2-methyladenine resulted in the accumulation of dysfunctional mitochondria with increased oxidant production, and as a consequence, inflammasome was activated [209]. Other mitochondrion-generated oxidants, such as $ONOO^-$ and $O_2^{\cdot-}$ can also activate the NLRP3 inflammasome [216, 217].

4.4. NLRP3 at the interface of inflammation and metabolism

The first link between inflammation and metabolism originated from early studies in models of obesity, where the expression of pro-inflammatory cytokines such as TNF-α, IL-6 and IL-1β was upregulated in adipose tissues of obese and diabetic subjects. The NLRP3 inflammasome, which regulates the secretion of IL-1β, is considered to be a sensor of altered metabolic homeostasis and its activation is thought to induce insulin resistance. Increased activity of NLRP3 was also implicated in the pathogenesis of metabolic diseases such as type 2 diabetes and metabolic syndrome [218], with insulin hypersensitivity being the primary phenotype of the NLRP3- or caspase-1-deficient mice [219, 220]. Interestingly, deficiency of IL-1β protects rodents from insulin resistance induced by high-fat diet [220, 221], and the treatment with an IL-1 receptor antagonist reduced hyperglycemia in diabetic rodents and improved glycemic control in type-2-diabetes patients [222, 223]. Studies using genetic mouse models demonstrated that IL-1β inhibits IIS by upregulating TNFα, a known insulin resistance-promoting cytokine [224, 225]. Although it is not clear whether or not the NLRP3 inflammasome contributes to neuronal insulin resistance, it is likely that a similar mechanism to that in adipose tissue might be prevalent in the CNS.

Conversely, metabolic signals (from mitochondria) can modulate inflammatory response. Mitochondrion-derived DAMPs, such as mtDNA, can directly induce inflammatory changes in microglial and neuronal cells [226], although the oxidation of mtDNA is still required [227], which supports the notion that redox control is the linking component transducing metabolic signal to inflammatory response. In addition, extracellular ATP at various concentrations can activate microglia and induce neuroprotective or neurotoxic effects by the expression of pro- or anti-inflammatory cytokines [228, 229].

4.5. Neuroinflammation in aging and Alzheimer's disease

Several of the inflammatory factors discussed above can be general neurotoxic factors in normal aging and neurodegenerative diseases. It is predicted that these inflammatory responses are partly driven by positive feedback loops between microglia and astrocytes. Amplification of inflammation by astrocytes worsens the neurotoxic environment and the damaged neurons can further activate glial cells by releasing ATP and other DAMPs. This encompasses a self-promoting cycle of inflammation and neuronal death, even after the withdrawal of initial stimuli. This inflammatory mechanism is hypothesized to cause neurodegeneration and set the foundation of neurological disorders such as AD [13].

Chronic, low-grade inflammation positively correlates with aging: with age, microglia exhibit enhanced sensitivity (priming) to inflammatory stimuli (originating either from peripheral tissues or brain), similar to that observed in brains with ongoing neurodegeneration [230]. In both physiologically aged and senescence-accelerated mouse models, profound microglia priming was characterized by increased basal production of pro-inflammatory cytokines (IL-1β, IL-6, and TNFα), decreased production of anti-inflammatory cytokines (IL-4 and IL-10), decreased activity of the TGFβ1-Smad3 signaling pathway, and upregulated TLR expression. This age-related increase in microglial activation negatively impacts brain function [231]. NLRP3-deficient mice on a high-fat diet showed lower incidence of astrogliosis as compared to the age-matched wildtype mice. Furthermore,

these NLRP3-deficient mice were significantly protected from age-related decline in cognition and memory [232]. The same study also suggested that IL-1β signaling, downstream of NLRP3 activation, modulates the age-related functional decline in the brain by the deletion of IL-1 receptor. Aging is also associated with dysregulation of microglia, with deficits in CD200 and fractalkine regulation. Similarly, astrocytes also exhibit pro-inflammatory phenotypes during aging: an increased expression of pro-inflammatory cytokines including TNF-α, IL-1β and IL-6 was observed in the rat cortex and striatum during aging [233].

In the Alzheimer's brain, Aβ is capable of activating microglia and astrocytes to induce production of damaging molecules such as H_2O_2, NO, pro-inflammatory cytokines, chemokines, and prostaglandins (*e.g.,* PGE2), which cause neuronal death [234]. Aβ plaques can be detected through several sensors, including TLRs, NLRs, and RAGE (receptor for advanced glycation end products) [204, 235–237]. Aβ oligomers and fibril-induced lysosomal damage can trigger activation of the NLRP3 inflammasome [201]. In neurons, NALP1, a member of the NLR family, can induce inflammatory response, similar to NLRP3 [238]. These inflammatory signals, along with other risk factors converge to produce an abnormal processing of the tau protein [239]. Although neuroinflammation can facilitate the formation of neurofibrillary tangles (NFTs) through tau kinases, it is not clear that whether these NFTs affect inflammatory responses [13, 240].

Despite the critical involvement of inflammatory processes in AD etiology, the use of anti-inflammatory drugs have produced minimum to no beneficial effects on symptomatic AD [241]. In these studies, anti-inflammatory drugs sometimes exhibit adverse effect in later stages of AD pathogenesis [241], although it was also found that long-term use of certain NSAIDs can reduce AD risk significantly with asymptomatic subjects [242, 243]. Interestingly, in another study, it was shown that AD risk reduction with NSAIDs only in participants having an APOE epsilon 4 allele [244], indicating the critical role of APOE status in AD-associated neuroinflammation. While the reasons for the failures in these epidemiological studies could be study design-based (such as the time and dose of intervention), one cannot ignore the fact that the pro-inflammatory environment in the AD brain is necessary for activating microglia- that clear Aβ [245], and even support neurogenesis after damage [246]. Therefore, it is hypothesized that anti-inflammatory drugs might only be beneficial in the early stages of AD (before the deposition of Aβ), direct evidence for which is yet to be seen [241].

5. Concluding remarks

Compromised glucose metabolism and mitochondrial function are signatures of normal brain aging and early stages of AD, while neuroinflammation is also observed in brain aging and the late stage of AD animal models and postmortem AD brains. It is still debatable whether or not neuroinflammation is the driven force of brain aging and AD or it is simply a consequence of metabolic dysfunction occurring earlier in the progression of aging or AD. It is noteworthy that although dysregulated neuroinflammation induces neurotoxicity and tissue damage, the primary function of controlled immune responses is still to protect the brain from infectious agent and injuries. Nevertheless, an increasing number of studies on

cell lines, genetic rodent models, and humans indicate that redox control might serve as a bidirectional link between energy metabolism and inflammatory responses in the brain. The brain metabolic-inflammatory axis entails interconnected cross-talks of energy metabolism, redox control, and neuroinflammation (Fig. 7) and might serve as an integrated mechanism for brain aging and Alzheimer's etiology.

Acknowledgments

Abbreviations

Aβ β-amyloid

AD Alzheimer's disease

Akt protein kinase B

AMPK 5′ adenosine monophosphate-activated protein kinase

AP-1 activator protein-1

APP amyloid precursor protein

ASK apoptosis signal-regulating kinase

DAMP damage-associated molecular pattern

ER endoplasmic reticulum

ERK extracellular signal-regulated kinase

GABA gamma-aminobutyric acid

GH growth hormone

GLUT glucose transporter

GPx glutathione peroxidase

HIF1-α hypoxia-inducible factor 1-α

IGF1 insulin-like factor 1

IIS insulin/IGF1 signaling

IKK IκB kinase

IRS insulin receptor substrate

JNK c-Jun N-terminal kinase

LTP long-term potentiation

MAPK mitogen-activated protein kinase

MCI	mild cognitive impairment
MPC	mitochondrial pyruvate carrier
MRI	magnetic resonance imaging
NAA	N-acetylaspartate
NFκB	nuclear factor kappa-light-chain-enhancer of activated B cells
NMR	nuclear magnetic resonance
NNT	nicotinamide nucleotide transhydrogenase
PAMP	pathogen-associated molecular pattern
PDH	pyruvate dehydrogenase
PET	positron emission tomography
PI3K	phosphatidylinositide 3-kinase
Prx	peroxiredoxins
PTEN	phosphatase and tensin homolog
TCA	tricarboxylic acid
Trx	thioredoxin
TrxR	thioredoxin reductase

References

1. Imtiaz B, Tolppanen AM, Kivipelto M, Soininen H. Future directions in Alzheimer's disease from risk factors to prevention. Biochem Pharmacol. 2014; 88:661–670. [PubMed: 24418410]

2. Rossi S, Zanier ER, Mauri I, Columbo A, Stocchetti N. Brain temperature, body core temperature, and intracranial pressure in acute cerebral damage. J Neurol Neurosurg Psychiatry. 2001; 71:448–454. [PubMed: 11561026]

3. Blass JP, Sheu RK, Gibson GE. Inherent abnormalities in energy metabolism in Alzheimer disease. Interaction with cerebrovascular compromise. Ann NY Acad Sci. 2000; 903:204–221. [PubMed: 10818509]

4. Swerdlow RH, Burns JM, Khan SM. The Alzheimer's disease mitochondrial cascade hypothesis. J Alzheimers Dis. 2010; 20(Suppl 2):S265–279. [PubMed: 20442494]

5. de la Monte S, Wands J. Review of insulin and insulin-like growth factor expression, signaling, and malfunction in the central nervous system: relevance to Alzheimer's disease. J Alzheimers Dis. 2005; 7:45–61. [PubMed: 15750214]

6. Harper S. Economic and social implications of aging societies. Science. 2014; 346:587–591. [PubMed: 25359967]

7. van Heemst D. Insulin, IGF-1 and longevity. Aging Dis. 2010; 1:147–157. [PubMed: 22396862]

8. Cheng Z, Tseng Y, White MF. Insulin signaling meets mitochondria in metabolism. Trends Endocrinol Metab. 2010; 21:589–598. [PubMed: 20638297]

9. Swerdlow RH. Brain aging, Alzheimer's disease, and mitochondria. Biochim Biophys Acta. 2011; 1812:1630–1639. [PubMed: 21920438]

10. De Felice FG, Ferreira ST. Inflammation, defective insulin signaling, and mitochondrial dysfunction as common molecular denominators connecting type 2 diabetes to Alzheimer disease. Diabetes. 2014; 63:2262–2272. [PubMed: 24931033]

11. Spielman LJ, Little JP, Klegeris A. Inflammation and insulin/IGF-1 resistance as the possible link between obesity and neurodegeneration. J Neuroimmunol. 2014; 273:8–21. [PubMed: 24969117]

12. Kapetanovic R, Bokil NJ, Sweet MJ. Innate immune perturbations, accumulating DAMPs and inflammasome dysregulation: A ticking time bomb in ageing. Ageing Res Rev. 2015; 24:40–53. [PubMed: 25725308]

13. Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH. Mechanisms underlying inflammation in neurodegeneration. Cell. 2010; 140:918–934. [PubMed: 20303880]

14. Jiang T, Cadenas E. Astrocytic metabolic and inflammatory changes as a function of age. Aging Cell. 2014; 13:1059–1067. [PubMed: 25233945]

15. Yin F, Boveris A, Cadenas E. Mitochondrial energy metabolism and redox signaling in brain aging and neurodegeneration. Antioxid Redox Signal. 2014; 20:353–371. [PubMed: 22793257]

16. Yin F, Sancheti H, Liu Z, Cadenas E. Mitochondrial function in ageing: coordination with signalling and transcriptional pathways. J Physiol. 2015:n/a–n/a.

17. Taneguchi CM, Emanuelli B, Kahn CR. Critical nodes in signalling pathways: insights into insulin action. Nature Mol Cell Biol. 2006; 7:85–96.

18. Cohen E, Dillin A. The insulin paradox: aging, proteotoxicity and neurodegeneration. Nat Rev Neurosci. 2008; 9:759–767. [PubMed: 18769445]

19. Yin F, Jiang T, Cadenas E. Metabolic triad in brain aging: mitochondria, insulin/IGF-1 signalling, and JNK signalling. Biochem Soc Trans. 2013; 41:101–105. [PubMed: 23356266]

20. Csiszar A, Wang M, Lakatta EG, Ungvari Z. Inflammation and endothelial dysfunction during aging: role of NF-κB. J Appl Physiol. 2008; 105:1333–1341. [PubMed: 18599677]

21. Lowell BB, Shulman GI. Mitochondrial dysfunction and type 2 diabetes. Science. 2005; 307:384–387. [PubMed: 15662004]

22. Havrankova J, Roth J, Brownstein MJ. Concentrations of insulin and insulin receptors in the brain are independent of peripheral insulin levels. Studies of obese and streptozotocin-treated rodents. J Clin Invest. 1979; 64:636–642. [PubMed: 156737]

23. van der Heide LP, Ramakers GM, Smidt MP. Insulin signaling in the central nervous system: learning to survive. Prog Neurobiol. 2006; 79:205–221. [PubMed: 16916571]

24. Grillo CA, Piroli GG, Hendry RM, Reagan LP. Insulin-stimulated translocation of GLUT4 to the plasma membrane in rat hippocampus is PI3-kinase dependent. Brain Res. 2009; 1296:35–45. [PubMed: 19679110]

25. Brüning J, Gautam D, Burks DJ, Gillette J, Schubert M, Orban PC, Klein R, Krone W, Müller-Wieland D, Kahn CR. Role of Brain Insulin Receptor in Control of Body Weight and Reproduction. Science. 2000; 289:2122–2125. [PubMed: 11000114]

26. Kenyon C, Chang J, Gensch E, Rudner A, Tabtiang RA. C. elegans mutant that lives twice as long as wild type. Nature. 1993; 366:461. [PubMed: 8247153]

27. Friedman DB, Johnson TE. A mutation in the age-1 gene in Caenorhabditis elegans lengthens life and reduces hermaphrodite fertility. Genetics. 1988; 118:75–86. [PubMed: 8608934]

28. Bluher M, Kahn BB, Kahn CR. Extended longevity in mice lacking the insulin receptor in adipose tissue. Science. 2003; 299:572–574. [PubMed: 12543978]

29. Taguchi A, Wartschow LM, White MF. Brain IRS2 Signaling Coordinates Life Span and Nutrient Homeostasis. Science. 2007; 317:369–372. [PubMed: 17641201]

30. Barzilai N, Ferrucci L. Insulin Resistance and Aging: A Cause or a Protective Response? J Gerontol A Biol Sci Med Sci. 2012

31. Mair W, Dillin A. Aging and survival: the genetics of life span extension by dietary restriction. Annu Rev Biochem. 2008; 77:727–754. [PubMed: 18373439]

32. Jiang T, Yin F, Yao J, Brinton RD, Cadenas E. Lipoic acid restores age-associated impairment of brain energy metabolism through the modulation of Akt/JNK signaling and PGC1a transcriptional pathway. Aging Cell. 2013; 12:1021–1031. [PubMed: 23815272]

33. Liu Z, Patil IY, Jiang T, Sancheti H, Walsh JP, Stiles BL, Yin F, Cadenas E. High-fat diet induces hepatic insulin resistance and impairment of synaptic plasticity. PLoS One. 2015; 10:e0128274. [PubMed: 26023930]

34. Sancheti H, Akopian G, Yin F, Brinton RD, Walsh JP, Cadenas E. Age-dependent modulation of synaptic plasticity and insulin mimetic effect of lipoic acid on a mouse model of Alzheimer's disease. PLoS One. 2013; 8:e69830. [PubMed: 23875003]

35. Ho L, Qin W, Pompl PN, Xiang Z, Wang J, Zhao Z, Peng Y, Cambareri G, Rocher A, Mobbs CV. Diet-induced insulin resistance promotes amyloidosis in a transgenic mouse model of Alzheimer's disease. FASEB J. 2004; 18:902–904. [PubMed: 15033922]

36. Plaschke K, Kopitz J, Siegelin M, Schliebs R, Salkovic-Petrisic M, Riederer P, Hoyer S. Insulin-resistant brain state after intracerebroventricular streptozotocin injection exacerbates Alzheimer-like changes in Tg2576 AbetaPP-overexpressing mice. J Alzheimers Dis. 2009; 19:691–704.

37. Cao D, Lu H, Lewis TL, Li L. Intake of sucrose-sweetened water induces insulin resistance and exacerbates memory deficits and amyloidosis in a transgenic mouse model of Alzheimer disease. J Biol Chem. 2007; 282:36275–36282. [PubMed: 17942401]

38. Talbot K, Wang HY, Kazi H, Han LY, Bakshi KP, Stucky A, Fuino RL, Kawaguchi KR, Samoyedny AJ, Wilson RS, Arvanitakis Z, Schneider JA, Wolf BA, Bennett DA, Trojanowski JQ, Arnold SE. Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. J Clin Invest. 2012; 122:1316–1338. [PubMed: 22476197]

39. Liu Y, Liu F, Grundke-Iqbal I, Iqbal K, Gong C-X. Deficient brain insulin signalling pathway in Alzheimer's disease and diabetes. J Pathol. 2011; 225:54–62. [PubMed: 21598254]

40. Kuusisto J, Koivisto K, Mykkänen L, Helkala EL, Vanhanen M, Hänninen T, Kervinen K, Kesäniemi YA, Riekkinen PJ, Laakso M. Association between features of the insulin resistance syndrome and alzheimer's disease independently of apolipoprotein e4 phenotype: cross sectional population based study. BMJ. 1997; 315:1045–1049. [PubMed: 9366728]

41. Craft S, Cholerton B, Baker LD. Insulin and Alzheimer's disease: untangling the web. J Alzheimers Dis. 2013; 33(Suppl 1):S263–275. [PubMed: 22936011]

42. Teune, LK.; Bartels, AL.; Leenders, KL. FDG-PET imaging in neurodegenerative brain diseases. In: Signorelli, F.; Chirchiglia, D., editors. Functional brain mapping and the endeavor to understand the working brain. Rijeka, Croatia: InTech; 2013.

43. Cunnane S, Nugent S, Roy M, Courchesne-Loyer A, Croteau E, Tremblay S, Castellano A, Pifferi F, Bocti C, Paquet N, Begdouri H, Bentourkia M, Turcotte E, Allard M, Barberger-Gateau P, Fulop T, Rapoport SI. Brain fuel metabolism, aging, and Alzheimer's disease. Nutrition. 2011; 27:3–20. [PubMed: 21035308]

44. Mergenthaler P, Lindauer U, Dienel GA, Meisel A. Sugar for the brain: the role of glucose in physiological and pathological brain function. Trends Neurosci. 2013; 36:587–597. [PubMed: 23968694]

45. Craft S. Insulin resistance syndrome and alzheimer disease: pathophysiologic mechanisms and therapeutic implications. Alzheimer Dis Assoc Disord. 2006; 20:298–301. [PubMed: 17132977]

46. Gage FH, Kelly PA, Bjorklund A. Regional changes in brain glucose metabolism reflect cognitive impairments in aged rats. J Neurosci. 1984; 4:2856–2865. [PubMed: 6502208]

47. Yin F, Yao J, Sancheti H, Feng T, Melcangi RC, Morgan TE, Finch CE, Pike CJ, Mack WJ, Cadenas E, Brinton RD. The perimenopausal aging transition in the female rat brain: decline in bioenergetic systems and synaptic plasticity. Neurobiol Aging. 2015; 36:2282–2295. [PubMed: 25921624]

48. Pardo JV, Lee JT, Sheikh SA, Surerus-Johnson C, Shah H, Munch KR, Carlis JV, Lewis SM, Kuskowski MA, Dysken MW. Where the brain grows old: Decline in anterior cingulate and medial prefrontal function with normal aging. Neuroimage. 2007; 35:1231–1237. [PubMed: 17321756]

49. Salat DH, Buckner RL, Snyder AZ, Greve DN, Desikan RS, Busa E, Morris JC, Dale AM, Fischl B. Thinning of the Cerebral Cortex in Aging. Cereb Cortex. 2004; 14:721–730. [PubMed: 15054051]

50. Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW. Mapping cortical change across the human life span. Nat Neurosci. 2003; 6:309–315. [PubMed: 12548289]

51. Kochunov P, Mangin JF, Coyle T, Lancaster J, Thompson P, Riviere D, Cointepas Y, Régis J, Schlosser A, Royall DR. Age-related morphology trends of cortical sulci. Hum Brain Mapp. 2005; 26:210–220. [PubMed: 16161162]

52. Mosconi L, Tsui WH, Herholz K, Pupi A, Drzezga A, Lucignani G, Reiman EM, Holthoff V, Kalbe E, Sorbi S, Diehl-Schmid J, Perneczky R, Clerici F, Caselli R, Beuthien-Baumann B, Kurz A, Minoshima S, de Leon MJ. Multicenter Standardized 18F-FDG PET Diagnosis of Mild Cognitive Impairment, Alzheimer's Disease, and Other Dementias. J Nucl Med. 2008; 49:390–398. [PubMed: 18287270]

53. Mosconi L, Tsui WH, Pupi A, De Santi S, Drzezga A, Minoshima S, de Leon MJ. 18F-FDG PET Database of Longitudinally Confirmed Healthy Elderly Individuals Improves Detection of Mild Cognitive Impairment and Alzheimer's Disease. J Nucl Med. 2007; 48:1129–1134. [PubMed: 17574982]

54. Alexander GE, Chen K, Pietrini P, Rapoport SI, Reiman EM. Longitudinal PET Evaluation of Cerebral Metabolic Decline in Dementia: A Potential Outcome Measure in Alzheimer's Disease Treatment Studies. Am J Psychiatry. 2002; 159:738–745. [PubMed: 11986126]

55. Mooradian AD, Morin AM, Cipp LJ, Haspel HC. Glucose transport is reduced in the blood-brain barrier of aged rats. Brain Res. 1991; 551:145–149. [PubMed: 1913147]

56. Hooijmans CR, Graven C, Dederen PJ, Tanila H, van Groen T, Kiliaan AJ. Amyloid beta deposition is related to decreased glucose transporter-1 levels and hippocampal atrophy in brains of aged APP/PS1 mice. Brain Res. 2007; 1181:93–103. [PubMed: 17916337]

57. Ding F, Yao J, Rettberg JR, Chen S, Brinton RD. Early decline in glucose transport and metabolism precedes shift to ketogenic system in female aging and Alzheimer's mouse brain: implication for bioenergetic intervention. PLoS One. 2013; 8:e79977. [PubMed: 24244584]

58. Simpson IA, Chundu KR, Davies-Hill T, Honer WG, Davies P. Decreased concentrations of GLUT1 and GLUT3 glucose transporters in the brains of patients with Alzheimer's disease. Ann Neurol. 1994; 35:546–551. [PubMed: 8179300]

59. Liu Y, Liu F, Iqbal K, Grundke-Iqbal I, Gong CX. Decreased glucose transporters correlate to abnormal hyperphosphorylation of tau in Alzheimer disease. FEBS Lett. 2008; 582:359–364. [PubMed: 18174027]

60. Harr SD, Simonian NA, Hyman BT. Functional Alterations in Alzheimer's Disease: Decreased Glucose Transporter 3 Immunoreactivity in the Perforant Pathway Terminal Zone. J Neuropathol Exp Neurol. 1995; 54:38–41. [PubMed: 7815078]

61. Kalaria RN, Harik SI. Reduced glucose transporter at the blood-brain barrier and in cerebral cortex in Alzheimer disease. J Neurochem. 1989; 53:1083–1088. [PubMed: 2769254]

62. Mangialasche F, Solomon A, Winblad B, Mecocci P, Kivipelto M. Alzheimer's disease: clinical trials and drug development. Lancet Neurol. 2010; 9:702–716. [PubMed: 20610346]

63. Magistretti, P.; Allaman, I. Brain Energy Metabolism. In: Pfaff, D., editor. Neuroscience in the 21st Century. Springer; New York: 2013. p. 1591-1620.

64. McCommis KS, Finck BN. Mitochondrial pyruvate transport: A historial perspective and future research directions. Biochem J. 2015; 466:443–454. [PubMed: 25748677]

65. Bender T, Martinou J-C. The mitochondrial pyruvate carrier in health and disease: To carry or not to carry? Biochim Biophys Acta. 2016 in press.

66. Sheu KF, Kim YT, Blass JP, Weksler ME. An immunochemical study of the pyruvate dehydrogenase deficit in Alzheimer's disease brain. Ann Neurol. 1985; 17:444–449. [PubMed: 4004169]

67. Nave K-A, Werner HB. Myelination of the nervous systems: mechanisms and functions. Annu Rev Cell Dev Biol. 2014; 30:503–533. [PubMed: 25288117]

68. Birsoy K, Wang T, Chen WW, Frinkman E, Abu-remaileh M, Sabatini DM. An essential role of the mitochondrial electron transport chain in cell proliferation is to enable aspartate synthesis. Cell. 2015; 162:540–551. [PubMed: 26232224]

69. Sullivan LB, Gui DY, Hosios AM, Bush LN, Frreinkman E, Vander Heiden MG. Supporting aspartate biosynthesis is an essential function of respiration in proliferating cells. Cell. 2015; 162:552–563. [PubMed: 26232225]

70. Bak LK, Schousboe A, Waagepetersen HS. The glutamate/GABA-glutamine cycle: aspects of transport, neurotransmitter homeostasis and ammonia transfer. J Neurochem. 2006; 98:641–653. [PubMed: 16787421]

71. Boumezbeur F, Mason GF, de Graaf RA, Behar KL, Cline GW, Shulman GI, Rothman DL, Petersen KF. Altered brain mitochondrial metabolism in healthy aging as assessed by in vivo magnetic resonance spectroscopy. J Cereb Blood Flow Metab. 2010; 30:211–221. [PubMed: 19794401]

72. Rothman DL, Behar KL, Hyder F, Shulman RG. In vivo NMR studies of the glutamate neurotransmitter flux and neuroenergetics: implications for brain function. Annu Rev Physiol. 2003; 65:401–427. [PubMed: 12524459]

73. Miccheli A, Puccetti C, Capuani G, Di Cocco ME, Giardino L, Calzà L, Battaglia A, Battistin L, Conti F. [1-13C]Glucose entry in neuronal and astrocytic intermediary metabolism of aged rats: A study of the effects of nicergoline treatment by 13C NMR spectroscopy. Brain Res. 2003; 966:116–125. [PubMed: 12646315]

74. Nomura Y, Yamanaka Y, Kitamura Y, Arima T, Ohnuki T, Oomura Y, Sasaki K, Nagashima K, Ihara Y. Senescence-accelerated mouse. Neurochemical studies on aging. Ann N Y Acad Sci. 1996; 786:410–418. [PubMed: 8687038]

75. Kondziella D, Hammer J, Sletvold O, Sonnewald U. The pentylenetetrazole-kindling model of epilepsy in SAMP8 mice: glial–neuronal metabolic interactions. Neurochem Int. 2003; 43:629–637. [PubMed: 12892650]

76. Hyder F, Patel AB, Gjedde A, Rothman DL, Behar KL, Shulman RG. Neuronal–Glial Glucose Oxidation and Glutamatergic–GABAergic Function. J Cereb Blood Flow Metab. 2006; 26:865–877. [PubMed: 16407855]

77. Dedeoglu A, Choi J-K, Cormier K, Kowall NW, Jenkins BG. Magnetic resonance spectroscopic analysis of Alzheimer's disease mouse brain that express mutant human APP shows altered neurochemical profile. Brain Res. 2004; 1012:60–65. [PubMed: 15158161]

78. Tiwari V, Patel AB. Impaired glutamatergic and GABAergic function at early age in AβPPswe-PS1dE9 mice: implications for Alzheimer's disease. J Alzheimers Dis. 2012; 28:765–769. [PubMed: 22112551]

79. Doert A, Pilatus U, Zanella F, Müller WE, Eckert GP. 1H-and 13C-NMR spectroscopy of Thy-1-APPSL mice brain extracts indicates metabolic changes in Alzheimer's disease. J Neural Transm (Vienna). 2015; 122:541–550. [PubMed: 25742870]

80. Sancheti H, Kanamori K, Patil I, Brinton RD, Ross BD, Cadenas E. Reversal of metabolic deficits by lipoic acid in a triple transgenic mouse model of Alzheimer's disease: A ^{13}C NMR study. J Cereb Blood Flow Metab. 2014; 34:288–296. [PubMed: 24220168]

81. Lin AP, Shic F, Enriquez C, Ross BD. Reduced glutamate neurotransmission in patients with Alzheimer's disease–an in vivo ^{13}C magnetic resonance spectroscopy study. MAGMA. 2003; 16:29–42. [PubMed: 12695884]

82. Sancheti H, Patil I, Kanamori K, Diaz Brinton R, Zhang W, Lin AL, Cadenas E. Hypermetabolic state in the 7-month-old triple transgenic mouse model of Alzheimer's disease and the effect of lipoic acid: a (13)C-NMR study. J Cereb Blood Flow Metab. 2014; 34:1749–1760. [PubMed: 25099753]

83. Nilsen LH, Rae C, Ittner LM, Götz J, Sonnewald U. Glutamate metabolism is impaired in transgenic mice with tau hyperphosphorylation. J Cereb Blood Flow Metab. 2013; 33:684–691. [PubMed: 23340677]

84. Drew B, Leeuwenburgh C. Ageing and subcellular distribution of mitochondria: role of mitochondrial DNA deletions and energy production. Acta Physiol Scand. 2004; 182:333–341. [PubMed: 15569094]

85. Navarro A, Boveris A. Mitochondrial nitric oxide synthase, mitochondrial brain dysfunction in aging, and mitochondria-targeted antioxidants. Adv Drug Deliv Rev. 2008; 60:1534–1544. [PubMed: 18647625]

86. Bowling AC, Mutisya EM, Walker LC, Price DL, Cork LC, Beal MF. Age-Dependent Impairment of Mitochondrial Function in Primate Brain. J Neurochem. 1993; 60:1964–1967. [PubMed: 8473911]

87. Petrosillo G, Matera M, Casanova G, Ruggiero FM, Paradies G. Mitochondrial dysfunction in rat brain with aging: Involvement of complex I, reactive oxygen species and cardiolipin. Neurochem Int. 2008; 53:126–131. [PubMed: 18657582]

88. Hauptmann S, Scherping I, Drose S, Brandt U, Schulz KL, Jendrach M, Leuner K, Eckert A, Muller WE. Mitochondrial dysfunction: an early event in Alzheimer pathology accumulates with age in AD transgenic mice. Neurobiol Aging. 2009; 30:1574–1586. [PubMed: 18295378]

89. Yao J, Irwin RW, Zhao L, Nilsen J, Hamilton RT, Brinton RD. Mitochondrial bioenergetic deficit precedes Alzheimer's pathology in female mouse model of Alzheimer's disease. Proc Natl Acad Sci USA. 2009; 106:14670–14675. [PubMed: 19667196]

90. Fukuyama R, Hatanpää K, Rapoport SI, Chandrasekaran K. Gene expression of ND4, a subunit of complex I of oxidative phosphorylation in mitochondria, is decreased in temporal cortex of brains of Alzheimer's disease patients. Brain Res. 1996; 713:290–293. [PubMed: 8725003]

91. Kim SH, Vlkolinsky R, Cairns N, Lubec G. Decreased levels of complex III core protein 1 and complex V β chain in brains from patients with Alzheimer's disease and Down syndrome. Cell Mol Life Sci. 2000; 57:1810–1816. [PubMed: 11130185]

92. Parker WDJ, Parks J, Filley CM, Kleinschmidt-DeMasters BK. Electron transport chain defects in Alzheimer's disease brain. Neurology. 1994; 44:1090. [PubMed: 8208407]

93. Kish SJ, Bergeron C, Rajput A, Dozic S, Mastrogiacomo F, Chang LJ, Wilson JM, DiStefano LM, Nobrega JN. Brain Cytochrome Oxidase in Alzheimer's Disease. J Neurochem. 1992; 59:776–779. [PubMed: 1321237]

94. Dragicevic N, Mamcarz M, Zhu Y, Buzzeo R, Tan J, Arendash GW, Bradshaw PC. Mitochondrial amyloid-beta levels are associated with the extent of mitochondrial dysfunction in different brain regions and the degree of cognitive impairment in Alzheimer's transgenic mice. J Alzheimers Dis. 2010; 20(Suppl 2):S535–550. [PubMed: 20463404]

95. Bobba A, Amadoro G, Valenti D, Corsetti V, Lassandro R, Atlante A. Mitochondrial respiratory chain Complexes I and IV are impaired by beta-amyloid via direct interaction and through Complex I-dependent ROS production, respectively. Mitochondrion. 2013; 13:298–311. [PubMed: 23562762]

96. Markesbery W. Oxidative Stress Hypothesis in Alzheimer's Disease. Free Radic Biol Med. 1997; 23:134–147. [PubMed: 9165306]

97. Lin M, Beal M. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature. 2006; 443:787–795. [PubMed: 17051205]

98. Boveris A, Cadenas E. Mitochondrial production of superoxide anions and its relationship to the antimycin-insensitive respiration. FEBS Lett. 1975; 54:311–314. [PubMed: 236930]

99. Boveris A, Cadenas E, Stoppani AOM. Role of ubiquinone in the mitochondrial generation of hydrogen peroxide. Biochem J. 1976; 156:435–444. [PubMed: 182149]

100. Cadenas E, Boveris A, Ragan CI, Stoppani AO. Production of superoxide radicals and hydrogen peroxide by NADH- ubiquinone reductase and ubiquinol-cytochrome c reductase from beef-heart mitochondria. Arch Biochem Biophys. 1977; 180:248–257. [PubMed: 195520]

101. Turrens JF. Mitochondrial formation of reactive oxygen species. J Physiol. 2003; 552:335–344. [PubMed: 14561818]

102. Rhee SG. Cell signaling: H2O2, a necessary evil for cell signaling. Science. 2006; 312:1882–1883. [PubMed: 16809515]

103. Storozhevykh TP, Senilova YE, Persiyantseva NA, Pinelis VG, Pomytkin IA. Mitochondrial respiratory chain is involved in insulin-stimulated hydrogen peroxide production and plays an integral role in insulin receptor autophosphorylation in neurons. BMC NeuroSci. 2007; 8:84. [PubMed: 17919343]

104. Persiyantseva NA, Storozhevykh TP, Senilova YE, Gorbacheva LR, Pinelis VG, Pomytkin IA. Mitochondrial H2O2 as an enable signal for triggering autophosphorylation of insulin receptor in neurons. J Mol Signal. 2013; 8:11. [PubMed: 24094269]

105. Loh K, Deng H, Fukushima A, Cai X, Boivin B, Galic S, Bruce C, Shields BJ, Skiba B, Ooms LM, Stepto N, Wu B, Mitchell CA, Tonks NK, Watt MJ, Febbraio MA, Crack PJ, Andrikopoulos S, Tiganis T. Reactive oxygen species enhance insulin sensitivity. Cell Metab. 2009; 10:260–272. [PubMed: 19808019]

106. Elchebly M, Payette P, Michaliszyn E, Cromlish W, Collins S, Loy AL, Normandin D, Cheng A, Himms-Hagen J, Chan CC, Ramachandran C, Gresser MJ, Tremblay ML, Kennedy BP. Increased insulin sensitivity and obesity resistance in mice lacking the protein tyrosine phosphatase-1B gene. Science. 1999; 283:1544–1548. [PubMed: 10066179]

107. Antico Arciuch VG, Galli S, Franco MC, Lam PY, Cadenas E, Carreras MC, Poderoso JJ. Akt1 intramitochondrial cycling is a crucial step in the redox modulation of cell cycle progression. PLoS One. 2009; 4:e7523. [PubMed: 19844585]

108. Iwakami S, Misu H, Takeda T, Sugimori M, Matsugo S, Kaneko S, Takamura T. Concentration-dependent dual effects of hydrogen peroxide on insulin signal transduction in H4IIEC hepatocytes. PLoS One. 2011; 6:e27401. [PubMed: 22102892]

109. Aguirre V, Uchida T, Yenush L, Davis R, White MF. The c-Jun NH(2)-terminal kinase promotes insulin resistance during association with insulin receptor substrate-1 and phosphorylation of Ser(307). J Biol Chem. 2000; 275:9047–9054. [PubMed: 10722755]

110. Zhou Q, Lam PY, Han D, Cadenas E. c-Jun N-terminal kinase regulates mitochondrial bioenergetics by modulating pyruvate dehydrogenase activity in primary cortical neurons. J Neurochem. 2008; 104:325–335. [PubMed: 17949412]

111. Nemoto S, Takeda K, Yu ZX, Ferrans VJ, Finkel T. Role for mitochondrial oxidants as regulators of cellular metabolism. Mol Cell Biol. 2000; 20:7311–7318. [PubMed: 10982848]

112. Yin F, Sancheti H, Cadenas E. Silencing of nicotinamide nucleotide transhydrogenase impairs cellular redox homeostasis and energy metabolism in PC12 cells. Biochim Biophys Acta. 2012; 1817:401–409. [PubMed: 22198343]

113. Pinzar E, Wang T, Garrido MR, Xu W, Levy P, Bottari SP. Angiotensin II induces tyrosine nitration and activation of ERK1/2 in vascular smooth muscle cells. FEBS Lett. 2005; 579:5100–5104. [PubMed: 16139272]

114. Saitoh M, Nishitoh H, Fujii M, Takeda K, Tobiume K, Sawada Y, Kawabata M, Miyazono K, Ichijo H. Mammalian thioredoxin is a direct inhibitor of apoptosis signal-regulating kinase (ASK) 1. EMBO J. 1998; 17:2596–2606. [PubMed: 9564042]

115. Foley TD, Armstrong JJ, Kupchak BR. Identification and H_2O_2 sensitivity of the major constitutive MAPK phosphatase from rat brain. Biochem Biophys Res Commun. 2004; 315:568–574. [PubMed: 14975738]

116. Adler V, Funchs SY, Benezra M, Rosario L, Tew KD, Pincus MR, Sardana M, Henderson CJ, Wolf CR, Davis RJ, Ronai Z. Regulation of JNK signaling by GSTp. EMBO J. 1999; 18:1321–1234. [PubMed: 10064598]

117. Barone E, Di Domenico F, Cassano T, Arena A, Tramutola A, Lavecchia MA, Coccia R, Butterfield DA, Perluigi M. Impairment of biliverdin reductase-A promotes brain insulin resistance in Alzheimer disease: A new paradigm. Free Radic Biol Med. 2016; 91:127–142. [PubMed: 26698666]

118. Tramutola A, Triplett JC, Di Domenico F, Niedowicz DM, Murphy MP, Coccia R, Perluigi M, Butterfield DA. Alteration of mTOR signaling occurs early in the progression of Alzheimer disease (AD): analysis of brain from subjects with pre-clinical AD, amnestic mild cognitive impairment and late-stage AD. J Neurochem. 2015; 133:739–749. [PubMed: 25645581]

119. Rhee SG, Woo HA. Multiple functions of peroxiredoxins: peroxidases, sensors and regulators of the intracellular messenger HO, and protein chaperones. Antioxid Redox Signal. 2011; 15:781–794. [PubMed: 20919930]

120. Dabkowski ER, Williamson CL, Hollander JM. Mitochondria-specific transgenic overexpression of phospholipid hydroperoxide glutathione peroxidase (GPx4) attenuates ischemia/reperfusion-associated cardiac dysfunction. Free Radic Biol Med. 2008; 45:855–865. [PubMed: 18638546]

121. Yoo MH, Gu X, Xu XM, Kim JY, Carlson BA, Patterson AD, Cai H, Gladyshev VN, Hatfield DL. Delineating the role of glutathione peroxidase 4 in protecting cells against lipid hydroperoxide damage and in Alzheimer's disease. Antioxid Redox Signal. 2010; 12:819–827. [PubMed: 19769463]

122. Shan X, Jones DP, Hashmi M, Anders MW. Selective depletion of mitochondrial glutathione concentrations by (R,S)-3-hydroxy-4-pentenoate potentiates oxidative cell death. Chem Res Toxicol. 1993; 6:75–81. [PubMed: 8448354]

123. Muyderman H, Nilsson M, Sims NR. Highly selective and prolonged depletion of mitochondrial glutathione in astrocytes markedly increases sensitivity to peroxynitrite. J Neurosci. 2004; 24:8019–8028. [PubMed: 15371502]

124. Wüllner U, Seyfried J, Groscurth P, Beinroth S, Winter S, Gleichmann M, Heneka M, Löschmann PA, Schulz JB, Weller M, Klockgether T. Glutathione depletion and neuronal cell death: the role of reactive oxygen intermediates and mitochondrial function. Brain Res. 1999; 826:53–62. [PubMed: 10216196]

125. Muyderman H, Wadey AL, Nilsson M, Sims NR. Mitochondrial glutathione protects against cell death induced by oxidative and nitrative stress in astrocytes. J Neurochem. 2007; 102:1369–1382. [PubMed: 17484727]

126. Jia Z, Zhu H, Misra HP, Li Y. Potent induction of total cellular GSH and NQO1 as well as mitochondrial GSH by 3H-1,2-dithiole-3-thione in SH-SY5Y neuroblastoma cells and primary human neurons: Protection against neurocytotoxicity elicited by dopamine, 6-hydroxydopamine, 4-hydroxy-2-nonenal, or hydrogen peroxide. Brain Res. 2008; 1197:159–169. [PubMed: 18234165]

127. Giustarini D, Dalle-Donne I, Milzani A, Rossi R. Low molecular mass thiols, disulfides and protein mixed disulfides in rat tissues: influence of sample manipulation, oxidative stress and ageing. Mech Ageing Dev. 2011; 132:141–148. [PubMed: 21335026]

128. Rebrin I, Kamzalov S, Sohal RS. Effects of age and caloric restriction on glutathione redox state in mice. Free Radic Biol Med. 2003; 35:626–635. [PubMed: 12957655]

129. Vina J, Sastre J, Anton V, Bruseghini L, Esteras A, Asensi M. Effect of aging on glutathione metabolism. Protection by antioxidants. EXS. 1992; 62:136–144. [PubMed: 1450581]

130. Asuncion J, Millan A, Pla R, Bruseghini L, Esteras A, Pallardo F, Sastre J, Vina J. Mitochondrial glutathione oxidation correlates with age-associated oxidative damage to mitochondrial DNA. FASEB J. 1996; 10:333–338. [PubMed: 8641567]

131. Emir UE, Raatz S, McPherson S, Hodges JS, Torkelson C, Tawfik P, White T, Terpstra M. Noninvasive quantification of ascorbate and glutathione concentration in the elderly human brain. NMR Biomed. 2011; 24:888–894. [PubMed: 21834011]

132. Cruz-Aguado R, Almaguer-Melian W, Diaz CM, Lorigados L, Bergado J. Behavioral and biochemical effects of glutathione depletion in the rat brain. Brain Res Bull. 2001; 55:327–333. [PubMed: 11489339]

133. Dean O, Bush AI, Berk M, Copolov DL, van den Buuse M. Glutathione depletion in the brain disrupts short-term spatial memory in the Y-maze in rats and mice. Behav Brain Res. 2009; 198:258–262. [PubMed: 19061918]

134. Zhang H, Go YM, Jones DP. Mitochondrial thioredoxin-2/peroxiredoxin-3 system functions in parallel with mitochondrial GSH system in protection against oxidative stress. Arch Biochem Biophys. 2007; 465:119–126. [PubMed: 17548047]

135. Peng Y, Yang PH, Guo Y, Ng SS, Liu J, Fung PC, Tay D, Ge J, He ML, Kung HF, Lin MC. Catalase and peroxiredoxin 5 protect Xenopus embryos against alcohol-induced ocular anomalies. Invest Ophth Vis Sci. 2004; 45:23–29.

136. Cox AG, Peskin AV, Paton LN, Winterbourn CC, Hampton MB. Redox potential and peroxide reactivity of human peroxiredoxin 3. Biochemistry. 2009; 48:6495–6501. [PubMed: 19462976]

137. Drechsel DA, Patel M. Respiration-dependent H2O2 removal in brain mitochondria via the thioredoxin/peroxiredoxin system. J Biol Chem. 2010; 285:27850–27858. [PubMed: 20558743]

138. Cox AG, Pearson AG, Pullar JM, Jonsson TJ, Lowther WT, Winterbourn CC, Hampton MB. Mitochondrial peroxiredoxin 3 is more resilient to hyperoxidation than cytoplasmic peroxiredoxins. Biochem J. 2009; 421:51–58. [PubMed: 19356151]

139. Rhee SG, Jeong W, Chang TS, Woo HA. Sulfiredoxin, the cysteine sulfinic acid reductase specific to 2-Cys peroxiredoxin: its discovery, mechanism of action, and biological significance. Kidney Int Suppl. 2007:S3–8. [PubMed: 17653208]

140. Noh YH, Baek JY, Jeong W, Rhee SG, Chang TS. Sulfiredoxin Translocation into Mitochondria Plays a Crucial Role in Reducing Hyperoxidized Peroxiredoxin III. J Biol Chem. 2009; 284:8470–8477. [PubMed: 19176523]

141. Musicco C, Capelli V, Pesce V, Timperio AM, Calvani M, Mosconi L, Zolla L, Cantatore P, Gadaleta MN. Accumulation of overoxidized Peroxiredoxin III in aged rat liver mitochondria. Biochim Biophys Acta. 2009; 1787:890–896. [PubMed: 19272351]

142. Ngo JK, Davies KJ. Importance of the lon protease in mitochondrial maintenance and the significance of declining lon in aging. Ann N Y Acad Sci. 2007; 1119:78–87. [PubMed: 18056957]

143. Hattori F, Murayama N, Noshita T, Oikawa S. Mitochondrial peroxiredoxin-3 protects hippocampal neurons from excitotoxic injury in vivo. J Neurochem. 2003; 86:860–868. [PubMed: 12887684]

144. Krapfenbauer K, Engidawork E, Cairns N, Fountoulakis M, Lubec G. Aberrant expression of peroxiredoxin subtypes in neurodegenerative disorders. Brain Res. 2003; 967:152–160. [PubMed: 12650976]

145. Kim SH, Fountoulakis M, Cairns N, Lubec G. Protein levels of human peroxiredoxin subtypes in brains of patients with Alzheimer's disease and Down syndrome. J Neural Transm Suppl. 2001:223–235. [PubMed: 11771746]

146. Chen L, Na R, Ran Q. Enhanced defense against mitochondrial hydrogen peroxide attenuates age-associated cognition decline. Neurobiol Aging. 2014; 35:2552–2561. [PubMed: 24906890]

147. Seo MS, Kang SW, Kim K, Baines IC, Lee TH, Rhee SG. Identification of a new type of mammalian peroxiredoxin that forms an intramolecular disulfide as a reaction intermediate. J Biol Chem. 2000; 275:20346–20354. [PubMed: 10751410]

148. Trujillo M, Clippe A, Manta B, Ferrer-Sueta G, Smeets A, Declercq JP, Knoops B, Radi R. Pre-steady state kinetic characterization of human peroxiredoxin 5: taking advantage of Trp84 fluorescence increase upon oxidation. Arch Biochem Biophys. 2007; 467:95–106. [PubMed: 17892856]

149. De Simoni S, Goemaere J, Knoops B. Silencing of peroxiredoxin 3 and peroxiredoxin 5 reveals the role of mitochondrial peroxiredoxins in the protection of human neuroblastoma SH-SY5Y cells toward MPP[+] Neurosci Lett. 2008; 433:219–224. [PubMed: 18262354]

150. Radyuk SN, Michalak K, Klichko VI, Benes J, Rebrin I, Sohal RS, Orr WC. Peroxiredoxin 5 confers protection against oxidative stress and apoptosis and also promotes longevity in Drosophila. Biochem J. 2009; 419:437–445. [PubMed: 19128239]

151. Banmeyer I, Marchand C, Clippe A, Knoops B. Human mitochondrial peroxiredoxin 5 protects from mitochondrial DNA damages induced by hydrogen peroxide. FEBS Lett. 2005; 579:2327–2333. [PubMed: 15848167]

152. Jarvis RM, Hughes SM, Ledgerwood EC. Peroxiredoxin 1 functions as a signal peroxidase to receive, transduce, and transmit peroxide signals in mammalian cells. Free Radic Biol Med. 2012; 53:1522–1530. [PubMed: 22902630]

153. Sobotta MC, Liou W, Stocker S, Talwar D, Oehler M, Ruppert T, Scharf AN, Dick TP. Peroxiredoxin-2 and STAT3 form a redox relay for H2O2 signaling. Nat Chem Biol. 2015; 11:64–70. [PubMed: 25402766]

154. Miranda-Vizuete A, Damdimopoulos AE, Spyrou G. The mitochondrial thioredoxin system. Antioxid Redox Signal. 2000; 2:801–810. [PubMed: 11213484]

155. Spyrou G, Enmark E, Miranda-Vizuete A, Gustafsson J. Cloning and expression of a novel mammalian thioredoxin. J Biol Chem. 1997; 272:2936–2941. [PubMed: 9006939]

156. Zhang R, Al-Lamki R, Bai L, Streb JW, Miano JM, Bradley J, Min W. Thioredoxin-2 inhibits mitochondria-located ASK1-mediated apoptosis in a JNK-independent manner. Circ Res. 2004; 94:1483–1491. [PubMed: 15117824]

157. Rojanathammanee L, Rakoczy S, Brown-Borg HM. Growth hormone alters the glutathione S-transferase and mitochondrial thioredoxin systems in long-living Ames dwarf mice. J Gerontol A Biol Sci Med Sci. 2014; 69:1199–1211. [PubMed: 24285747]

158. Arodin L, Lamparter H, Karlsson H, Nennesmo I, Bjornstedt M, Schroder J, Fernandes AP. Alteration of thioredoxin and glutaredoxin in the progression of Alzheimer's disease. J Alzheimers Dis. 2014; 39:787–797. [PubMed: 24270206]

159. Rohrbach S, Gruenler S, Teschner M, Holtz J. The thioredoxin system in aging muscle: key role of mitochondrial thioredoxin reductase in the protective effects of caloric restriction? Am J Physiol Regul Integr Comp Physiol. 2006; 291:R927–R935. [PubMed: 16675629]

160. Patenaude A, Ven Murthy MR, Mirault ME. Mitochondrial thioredoxin system: effects of TrxR2 overexpression on redox balance, cell growth, and apoptosis. J Biol Chem. 2004; 279:27302–27314. [PubMed: 15082714]

161. Rydstrom J. Mitochondrial NADPH, transhydrogenase, and disease. Biochim Biophys Acta. 2006; 1757:721–726. [PubMed: 16730324]

162. Hoek JB, Rydström J. Physiological roles of nicotinamide nucleotide transhydrogenase. Biochem J. 1988; 254:1–10. [PubMed: 3052428]

163. Agarwal AR, Zhao L, Sancheti H, Sundar IK, Rahman I, Cadenas E. Short-term cigarette smoke exposure induces reversible changes in energy metabolism and cellular redox status independent of inflammatory responses in mouse lungs. Am J Physiol-Lung C. 2012; 303:L889–898.

164. Lopert P, Patel M. Nicotinamide nucleotide transhydrogenase (Nnt) links the substrate requirement in brain mitochondria for hydrogen peroxide removal to the thioredoxin/peroxiredoxin (Trx/Prx) system. J Biol Chem. 2014; 289:15611–15620. [PubMed: 24722990]

165. Ghosh D, Levault KR, Brewer GJ. Relative importance of redox buffers GSH and NAD(P)H in age-related neurodegeneration and Alzheimer disease-like mouse neurons. Aging Cell. 2014; 13:631–640. [PubMed: 24655393]

166. Nickel AG, von Hardenberg A, Hohl M, Loffler JR, Kohlhaas M, Becker J, Reil JC, Kazakov A, Bonnekoh J, Stadelmaier M, Puhl SL, Wagner M, Bogeski I, Cortassa S, Kappl R, Pasieka B, Lafontaine M, Lancaster CR, Blacker TS, Hall AR, Duchen MR, Kastner L, Lipp P, Zeller T, Muller C, Knopp A, Laufs U, Bohm M, Hoth M, Maack C. Reversal of Mitochondrial Transhydrogenase Causes Oxidative Stress in Heart Failure. Cell Metab. 2015; 22:472–484. [PubMed: 26256392]

167. Han D, Canali R, Garcia J, Aguilera R, Gallaher TK, Cadenas E. Sites and mechanisms of aconitase inactivation by peroxynitrite: modulation by citrate and glutathione. Biochemistry. 2005; 44:11986–11996. [PubMed: 16142896]

168. Nulton-Persson AC, Starke DW, Mieyal JJ, Szweda LI. Reversible inactivation of alpha-ketoglutarate dehydrogenase in response to alterations in the mitochondrial glutathione status. Biochemistry. 2003; 42:4235–4242. [PubMed: 12680778]

169. Reed T, Perluigi M, Sultana R, Pierce WM, Klein JB, Turner DM, Coccia R, Markesbery WR, Butterfield DA. Redox proteomic identification of 4-hydroxy-2-nonenal-modified brain proteins in amnestic mild cognitive impairment: insight into the role of lipid peroxidation in the progression and pathogenesis of Alzheimer's disease. Neurobiol Dis. 2008; 30:107–120. [PubMed: 18325775]

170. Garcia J, Han D, Sancheti H, Yap LP, Kaplowitz N, Cadenas E. Regulation of mitochondrial glutathione redox status and protein glutathionylation by respiratory substrates. J Biol Chem. 2010; 285:39646–39654. [PubMed: 20937819]

171. Lam PY, Yin F, Hamilton RT, Boveris A, Cadenas E. Elevated neuronal nitric oxide synthase expression during ageing and mitochondrial energy production. Free Radic Res. 2009; 43:431–439. [PubMed: 19347761]

172. Taylor ER, Hurrell F, Shannon RJ, Lin TK, Hirst J, Murphy MP. Reversible glutathionylation of complex I increases mitochondrial superoxide formation. J Biol Chem. 2003; 278:19603–19610. [PubMed: 12649289]

173. Chen YR, Chen CL, Pfeiffer DR, Zweier JL. Mitochondrial complex II in the post-ischemic heart: oxidative injury and the role of protein S-glutathionylation. J Biol Chem. 2007; 282:32640–32654. [PubMed: 17848555]

174. Bubber P, Haroutunian V, Fisch G, Blass JP, Gibson GE. Mitochondrial abnormalities in Alzheimer brain: mechanistic implications. Ann Neurol. 2005; 57:695–703. [PubMed: 15852400]

175. Sultana R, Butterfield DA. Oxidatively modified, mitochondria-relevant brain proteins in subjects with Alzheimer disease and mild cognitive impairment. J Bioenerg Biomembr. 2009; 41:441–446. [PubMed: 19777328]

176. Agarwal AR, Yin F, Cadenas E. Short-term cigarette smoke exposure leads to metabolic alterations in lung alveolar cells. Am J Respir Cell Mol. 2014; 51:284–293.

177. Agarwal AR, Yin F, Cadenas E. Metabolic shift in lung alveolar cell mitochondria following acrolein exposure. Am J Physiol Lung Cell Mol Physiol. 2013; 305:L764–773. [PubMed: 24056970]

178. Carson MJ, Doose JM, Melchior B, Schmid CD, Ploix CC. CNS immune privilege: hiding in plain sight. Immunol Rev. 2006; 213:48–65. [PubMed: 16972896]

179. Farina C, Aloisi F, Meinl E. Astrocytes are active players in cerebral innate immunity. Trends Immunol. 2007; 28:138–145. [PubMed: 17276138]

180. Zhang G, Li J, Purkayastha S, Tang Y, Zhang H, Yin Y, Li B, Liu G, Cai D. Hypothalamic programming of systemic ageing involving IKK-beta, NF-kappaB and GnRH. Nature. 2013; 497:211–216. [PubMed: 23636330]

181. Janssen-Heininger YM, Poynter ME, Baeuerle PA. Recent advances towards understanding redox mechanisms in the activation of nuclear factor kappaB. Free Radic Biol Med. 2000; 28:1317–1327. [PubMed: 10924851]

182. Kabe Y, Ando K, Hirao S, Yoshida M, Handa H. Redox regulation of NF-kappaB activation: distinct redox regulation between the cytoplasm and the nucleus. Antioxid Redox Signal. 2005; 7:395–403. [PubMed: 15706086]

183. Weinberg SE, Sena LA, Chandel NS. Mitochondria in the Regulation of Innate and Adaptive Immunity. Immunity. 2015; 42:406–417. [PubMed: 25786173]

184. Patten DA, Germain M, Kelly MA, Slack RS. Reactive oxygen species: stuck in the middle of neurodegeneration. J Alzheimers Dis. 2010; 20(Suppl 2):S357–367. [PubMed: 20421690]

185. Takada Y, Mukhopadhyay A, Kundu GC, Mahabeleshwar GH, Singh S, Aggarwal BB. Hydrogen peroxide activates NF-kappa B through tyrosine phosphorylation of I kappa B alpha and serine phosphorylation of p65: evidence for the involvement of I kappa B alpha kinase and Syk protein-tyrosine kinase. J Biol Chem. 2003; 278:24233–24241. [PubMed: 12711606]

186. Pahl HL. Activators and target genes of Rel/NF-kappaB transcription factors. Oncogene. 1999; 18:6853–6866. [PubMed: 10602461]

187. Das KC, Lewis-Molock Y, White CW. Activation of NF-kappa B and elevation of MnSOD gene expression by thiol reducing agents in lung adenocarcinoma (A549) cells. Am J Physiol. 1995; 269:L588–602. [PubMed: 7491977]

188. Bubici C, Papa S, Dean K, Franzoso G. Mutual cross-talk between reactive oxygen species and nuclear factor-kappa B: molecular basis and biological significance. Oncogene. 2006; 25:6731–6748. [PubMed: 17072325]

189. Song YS, Park HJ, Kim SY, Lee SH, Yoo HS, Lee HS, Lee MK, Oh KW, Kang SK, Lee SE, Hong JT. Protective role of Bcl-2 on beta-amyloid-induced cell death of differentiated PC12 cells: reduction of NF-kappaB and p38 MAP kinase activation. Neurosci Res. 2004; 49:69–80. [PubMed: 15099705]

190. Chongthammakun V, Sanvarinda Y, Chongthammakun S. Reactive oxygen species production and MAPK activation are implicated in tetrahydrobiopterin-induced SH-SY5Y cell death. Neurosci Lett. 2009; 449:178–182. [PubMed: 19013215]

191. Chen L, Liu L, Yin J, Luo Y, Huang S. Hydrogen peroxide-induced neuronal apoptosis is associated with inhibition of protein phosphatase 2A and 5, leading to activation of MAPK pathway. Int J Biochem Cell Biol. 2009; 41:1284–1295. [PubMed: 19038359]

192. Patel JR, Brewer GJ. Age-related differences in NFkappaB translocation and Bcl-2/Bax ratio caused by TNFalpha and Abeta42 promote survival in middle-age neurons and death in old neurons. Exp Neurol. 2008; 213:93–100. [PubMed: 18625500]

193. Strowig T, Henao-Mejia J, Elinav E, Flavell R. Inflammasomes in health and disease. Nature. 2012; 481:278–286. [PubMed: 22258606]

194. Walsh JG, Muruve DA, Power C. Inflammasomes in the CNS. Nat Rev Neurosci. 2014; 15:84–97. [PubMed: 24399084]

195. Abais JM, Xia M, Zhang Y, Boini KM, Li PL. Redox regulation of NLRP3 inflammasomes: ROS as trigger or effector? Antioxid Redox Signal. 2015; 22:1111–1129. [PubMed: 25330206]

196. Rathinam VA, Vanaja SK, Fitzgerald KA. Regulation of inflammasome signaling. Nature immunology. 2012; 13:333–342. [PubMed: 22430786]

197. Minkiewicz J, de Rivero Vaccari JP, Keane RW. Human astrocytes express a novel NLRP2 inflammasome. Glia. 2013; 61:1113–1121. [PubMed: 23625868]

198. Kahlenberg JM, Dubyak GR. Mechanisms of caspase-1 activation by P2X7 receptor-mediated K+ release. Am J Physiol Cell Physiol. 2004; 286:C1100–1108. [PubMed: 15075209]

199. Kanneganti TD, Lamkanfi M, Kim YG, Chen G, Park JH, Franchi L, Vandenabeele P, Nunez G. Pannexin-1-mediated recognition of bacterial molecules activates the cryopyrin inflammasome independent of Toll-like receptor signaling. Immunity. 2007; 26:433–443. [PubMed: 17433728]

200. Hornung V, Bauernfeind F, Halle A, Samstad EO, Kono H, Rock KL, Fitzgerald KA, Latz E. Silica crystals and aluminum salts activate the NALP3 inflammasome through phagosomal destabilization. Nat Immunol. 2008; 9:847–856. [PubMed: 18604214]

201. Halle A, Hornung V, Petzold GC, Stewart CR, Monks BG, Reinheckel T, Fitzgerald KA, Latz E, Moore KJ, Golenbock DT. The NALP3 inflammasome is involved in the innate immune response to amyloid-beta. Nat Immunol. 2008; 9:857–865. [PubMed: 18604209]

202. Zhou R, Tardivel A, Thorens B, Choi I, Tschopp J. Thioredoxin-interacting protein links oxidative stress to inflammasome activation. Nat Immunol. 2010; 11:136–140. [PubMed: 20023662]

203. Petrilli V, Papin S, Dostert C, Mayor A, Martinon F, Tschopp J. Activation of the NALP3 inflammasome is triggered by low intracellular potassium concentration. Cell Death Differ. 2007; 14:1583–1589. [PubMed: 17599094]

204. Tschopp J, Schroder K. NLRP3 inflammasome activation: The convergence of multiple signalling pathways on ROS production? Nature reviews. Immunology. 2010; 10:210–215.

205. Spindel ON, Berk BC. Redox redux: protecting the ischemic myocardium. J Clin Invest. 2012; 122:30–32. [PubMed: 22201673]

206. Dostert C, Petrilli V, Van Bruggen R, Steele C, Mossman BT, Tschopp J. Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica. Science. 2008; 320:674–677. [PubMed: 18403674]

207. Meissner F, Molawi K, Zychlinsky A. Superoxide dismutase 1 regulates caspase-1 and endotoxic shock. Nat Immunol. 2008; 9:866–872. [PubMed: 18604212]

208. Cruz CM, Rinna A, Forman HJ, Ventura AL, Persechini PM, Ojcius DM. ATP activates a reactive oxygen species-dependent oxidative stress response and secretion of proinflammatory cytokines in macrophages. J Biol Chem. 2007; 282:2871–2879. [PubMed: 17132626]

209. Zhou R, Yazdi AS, Menu P, Tschopp J. A role for mitochondria in NLRP3 inflammasome activation. Nature. 2011; 469:221–225. [PubMed: 21124315]

210. Infanger DW, Sharma RV, Davisson RL. NADPH oxidases of the brain: distribution, regulation, and function. Antioxid Redox Signal. 2006; 8:1583–1596. [PubMed: 16987013]

211. Shimohama S, Tanino H, Kawakami N, Okamura N, Kodama H, Yamaguchi T, Hayakawa T, Nunomura A, Chiba S, Perry G, Smith MA, Fujimoto S. Activation of NADPH oxidase in Alzheimer's disease brains. Biochem Biophys Res Commun. 2000; 273:5–9. [PubMed: 10873554]

212. Bruce-Keller AJ, White CL, Gupta S, Knight AG, Pistell PJ, Ingram DK, Morrison CD, Keller JN. NOX activity in brain aging: exacerbation by high fat diet. Free Radic Biol Med. 2010; 49:22–30. [PubMed: 20347034]

213. Zawada WM, Banninger GP, Thornton J, Marriott B, Cantu D, Rachubinski AL, Das M, Griffin WS, Jones SM. Generation of reactive oxygen species in 1-methyl-4-phenylpyridinium (MPP+) treated dopaminergic neurons occurs as an NADPH oxidase-dependent two-wave cascade. J Neuroinflammation. 2011; 8:129. [PubMed: 21975039]

214. Han D, Antunes F, Canali R, Rettori D, Cadenas E. Voltage-dependent anion channels control the release of superoxide anion from mitochondria to cytosol. J Biol Chem. 2003; 278:5557–5563. [PubMed: 12482755]

215. Sultana R, Poon HF, Cai J, Pierce WM, Merchant M, Klein JB, Markesbery WR, Butterfield DA. Identification of nitrated proteins in Alzheimer's disease brain using a redox proteomics approach. Neurobiol Dis. 2006; 22:76–87. [PubMed: 16378731]

216. Hewinson J, Moore SF, Glover C, Watts AG, MacKenzie AB. A key role for redox signaling in rapid P2X7 receptor-induced IL-1 beta processing in human monocytes. J Immunol. 2008; 180:8410–8420. [PubMed: 18523309]

217. Abais JM, Xia M, Li G, Gehr TW, Boini KM, Li PL. Contribution of endogenously produced reactive oxygen species to the activation of podocyte NLRP3 inflammasomes in hyperhomocysteinemia. Free Radic Biol Med. 2014; 67:211–220. [PubMed: 24140862]

218. Haneklaus M, O'Neill LA. NLRP3 at the interface of metabolism and inflammation. Immunol Rev. 2015; 265:53–62. [PubMed: 25879283]

219. Vandanmagsar B, Youm YH, Ravussin A, Galgani JE, Stadler K, Mynatt RL, Ravussin E, Stephens JM, Dixit VD. The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. Nature medicine. 2011; 17:179–188.

220. Wen H, Gris D, Lei Y, Jha S, Zhang L, Huang MT, Brickey WJ, Ting JP. Fatty acid-induced NLRP3-ASC inflammasome activation interferes with insulin signaling. Nat Immunol. 2011; 12:408–415. [PubMed: 21478880]

221. Stienstra R, Joosten LA, Koenen T, van Tits B, van Diepen JA, van den Berg SA, Rensen PC, Voshol PJ, Fantuzzi G, Hijmans A, Kersten S, Muller M, van den Berg WB, van Rooijen N, Wabitsch M, Kullberg BJ, van der Meer JW, Kanneganti T, Tack CJ, Netea MG. The inflammasome-mediated caspase-1 activation controls adipocyte differentiation and insulin sensitivity. Cell metabolism. 2010; 12:593–605. [PubMed: 21109192]

222. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. Nature reviews. Immunology. 2011; 11:98–107.

223. Ehses JA, Lacraz G, Giroix MH, Schmidlin F, Coulaud J, Kassis N, Irminger JC, Kergoat M, Portha B, Homo-Delarche F, Donath MY. IL-1 antagonism reduces hyperglycemia and tissue inflammation in the type 2 diabetic GK rat. Proc Natl Acad Sci USA. 2009; 106:13998–14003. [PubMed: 19666548]

224. Jager J, Gremeaux T, Cormont M, Le Marchand-Brustel Y, Tanti JF. Interleukin-1beta-induced insulin resistance in adipocytes through down-regulation of insulin receptor substrate-1 expression. Endocrinology. 2007; 148:241–251. [PubMed: 17038556]

225. Hotamisligil GS, Peraldi P, Budavari A, Ellis R, White MF, Spiegelman BM. IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-alpha- and obesity-induced insulin resistance. Science. 1996; 271:665–668. [PubMed: 8571133]

226. Wilkins HM, Carl SM, Weber SG, Ramanujan SA, Festoff BW, Linseman DA, Swerdlow RH. Mitochondrial lysates induce inflammation and Alzheimer's disease-relevant changes in microglial and neuronal cells. J Alzheimers Dis. 2015; 45:305–318. [PubMed: 25537010]

227. Shimada K, Crother TR, Karlin J, Dagvadorj J, Chiba N, Chen S, Ramanujan VK, Wolf AJ, Vergnes L, Ojcius DM, Rentsendorj A, Vargas M, Guerrero C, Wang Y, Fitzgerald KA, Underhill DM, Town T, Arditi M. Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. Immunity. 2012; 36:401–414. [PubMed: 22342844]

228. Inoue K. Microglial activation by purines and pyrimidines. Glia. 2002; 40:156–163. [PubMed: 12379903]

229. Davalos D, Grutzendler J, Yang G, Kim JV, Zuo Y, Jung S, Littman DR, Dustin ML, Gan WB. ATP mediates rapid microglial response to local brain injury in vivo. Nat Neurosci. 2005; 8:752–758. [PubMed: 15895084]

230. Norden DM, Godbout JP. Review: microglia of the aged brain: primed to be activated and resistant to regulation. Neuropathology and applied neurobiology. 2013; 39:19–34. [PubMed: 23039106]

231. Czirr E, Wyss-Coray T. The immunology of neurodegeneration. J Clin Invest. 2012; 122:1156–1163. [PubMed: 22466657]

232. Youm YH, Grant RW, McCabe LR, Albarado DC, Nguyen KY, Ravussin A, Pistell P, Newman S, Carter R, Laque A, Munzberg H, Rosen CJ, Ingram DK, Salbaum JM, Dixit VD. Canonical Nlrp3 inflammasome links systemic low-grade inflammation to functional decline in aging. Cell Metab. 2013; 18:519–532. [PubMed: 24093676]

233. Campuzano O, Castillo-Ruiz MM, Acarin L, Castellano B, Gonzalez B. Increased levels of proinflammatory cytokines in the aged rat brain attenuate injury-induced cytokine response after excitotoxic damage. J Neurosci Res. 2009; 87:2484–2497. [PubMed: 19326443]

234. Kitazawa M, Yamasaki TR, LaFerla FM. Microglia as a potential bridge between the amyloid beta-peptide and tau. Ann N Y Acad Sci. 2004; 1035:85–103. [PubMed: 15681802]

235. Richard KL, Filali M, Prefontaine P, Rivest S. Toll-like receptor 2 acts as a natural innate immune receptor to clear amyloid beta 1–42 and delay the cognitive decline in a mouse model of Alzheimer's disease. J Neurosci. 2008; 28:5784–5793. [PubMed: 18509040]

236. Reed-Geaghan EG, Savage JC, Hise AG, Landreth GE. CD14 and toll-like receptors 2 and 4 are required for fibrillar A{beta}-stimulated microglial activation. J Neurosci. 2009; 29:11982–11992. [PubMed: 19776284]

237. Neeper M, Schmidt AM, Brett J, Yan SD, Wang F, Pan YC, Elliston K, Stern D, Shaw A. Cloning and expression of a cell surface receptor for advanced glycosylation end products of proteins. J Biol Chem. 1992; 267:14998–15004. [PubMed: 1378843]

238. Schroder K, Tschopp J. The inflammasomes. Cell. 2010; 140:821–832. [PubMed: 20303873]

239. Maccioni RB, Rojo LE, Fernandez JA, Kuljis RO. The role of neuroimmunomodulation in Alzheimer's disease. Ann N Y Acad Sci. 2009; 1153:240–246. [PubMed: 19236346]

240. Ballatore C, Lee VM, Trojanowski JQ. Tau-mediated neurodegeneration in Alzheimer's disease and related disorders. Nat Rev Neurosci. 2007; 8:663–672. [PubMed: 17684513]

241. Imbimbo BP, Solfrizzi V, Panza F. Are NSAIDs useful to treat Alzheimer's disease or mild cognitive impairment? Front Aging Neurosci. 2010; 2

242. Vlad SC, Miller DR, Kowall NW, Felson DT. Protective effects of NSAIDs on the development of Alzheimer disease. Neurology. 2008; 70:1672–1677. [PubMed: 18458226]

243. Breitner JC, Baker LD, Montine TJ, Meinert CL, Lyketsos CG, Ashe KH, Brandt J, Craft S, Evans DE, Green RC, Ismail MS, Martin BK, Mullan MJ, Sabbagh M, Tariot PN, Group AR. Extended results of the Alzheimer's disease anti-inflammatory prevention trial. Alzheimers Dement. 2011; 7:402–411. [PubMed: 21784351]

244. Szekely CA, Breitner JC, Fitzpatrick AL, Rea TD, Psaty BM, Kuller LH, Zandi PP. NSAID use and dementia risk in the Cardiovascular Health Study: role of APOE and NSAID type. Neurology. 2008; 70:17–24. [PubMed: 18003940]

245. Lai AY, McLaurin J. Clearance of amyloid-beta peptides by microglia and macrophages: the issue of what, when and where. Future Neurol. 2012; 7:165–176. [PubMed: 22737039]

246. Thored P, Heldmann U, Gomes-Leal W, Gisler R, Darsalia V, Taneera J, Nygren JM, Jacobsen SE, Ekdahl CT, Kokaia Z, Lindvall O. Long-term accumulation of microglia with proneurogenic phenotype concomitant with persistent neurogenesis in adult subventricular zone after stroke. Glia. 2009; 57:835–849. [PubMed: 19053043]
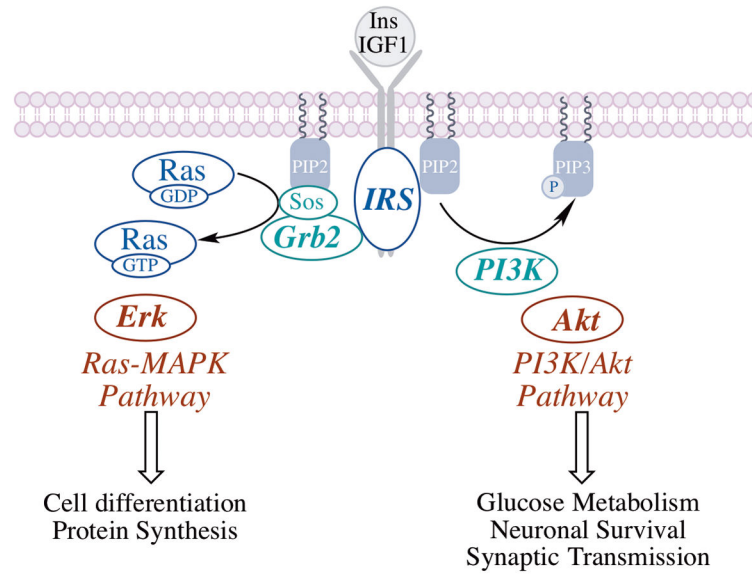
Fig. 1. Insulin/IGF1 signaling (IIS) is primarily orchestrated through insulin and IGF1 and the PI3K/Akt and ERK1/2 signaling pathways

Binding of the ligand to insulin receptor or IGF1 receptor activates the insulin receptor substrate (IRS). Binding of PI3K to the phosphorylated IRS activates the PI3K/Akt signaling network, whereas recruitment of Grb2 to the IRS results in Sos-mediated activation of the Ras-MAPK pathway. The PI3K/Akt pathway effects changes in carbohydrate and lipid metabolism and modulates glucose uptake, whereas the Ras-MAPK pathway is involved in cell growth and differentiation and protein synthesis.
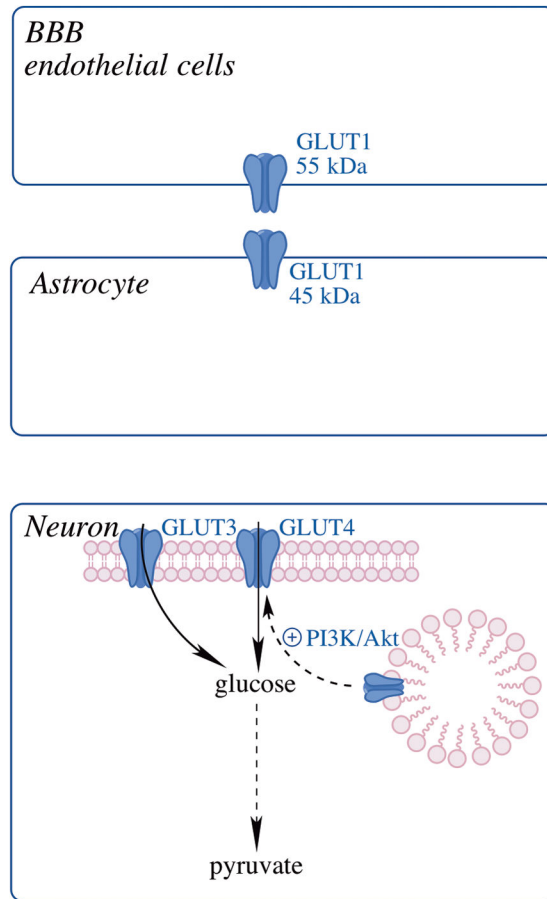
Fig. 2. Glucose transporters (GLUTs) in the brain
GLUT1 (55kDa) is expressed in endothelial cells of the BBB; GLUT1 (45kDa)-mediated transport of glucose into astrocytes; glucose uptake into neurons via neuronal GLUTs, GLUT3 and the insulin-sensitive GLUT4.
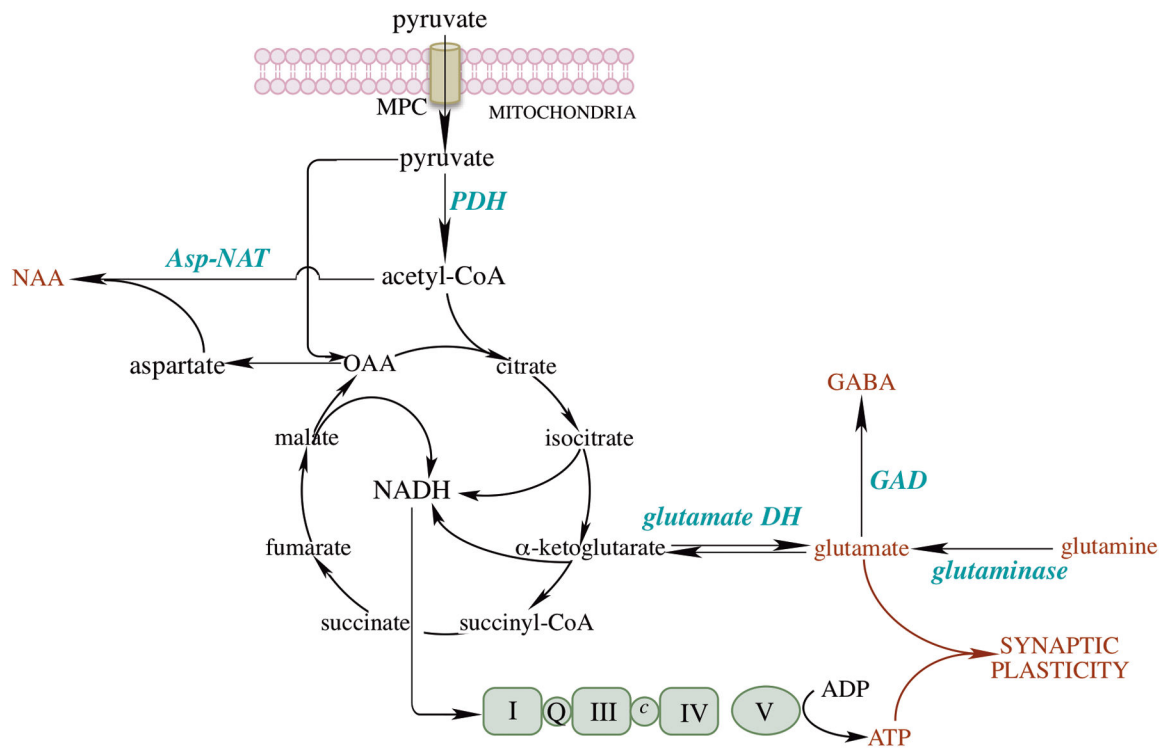
Fig. 3. Mitochondrial energy metabolism in brain

Pyruvate imported by the mitochondrial pyruvate carrier (MPC) is converted to acetyl-CoA, which enters the TCA cycle to generate NADH, the reducing equivalents of which flow through the respiratory chain and oxidative phosphorylation. ATP generated by oxidative phosphorylation together with glutamate and GABA are critical for synaptic plasticity in brain. Glutamate is primarily generated from (a) α-ketoglutarate by glutamate dehydrogenase and (b) astrocyte-originated glutamine by glutaminase. GABA is produced by glutamate decarboxylase from glutamate. Acetyl-CoA is also a co-substrate for the synthesis of N-acetylaspartate (NAA) by aspartate N-acetyltransferase (Asp-NAT). Aspartate generated from oxaloacetate (coupled to the conversion of glutamate to α-ketoglutarate) is critical in cell proliferation.
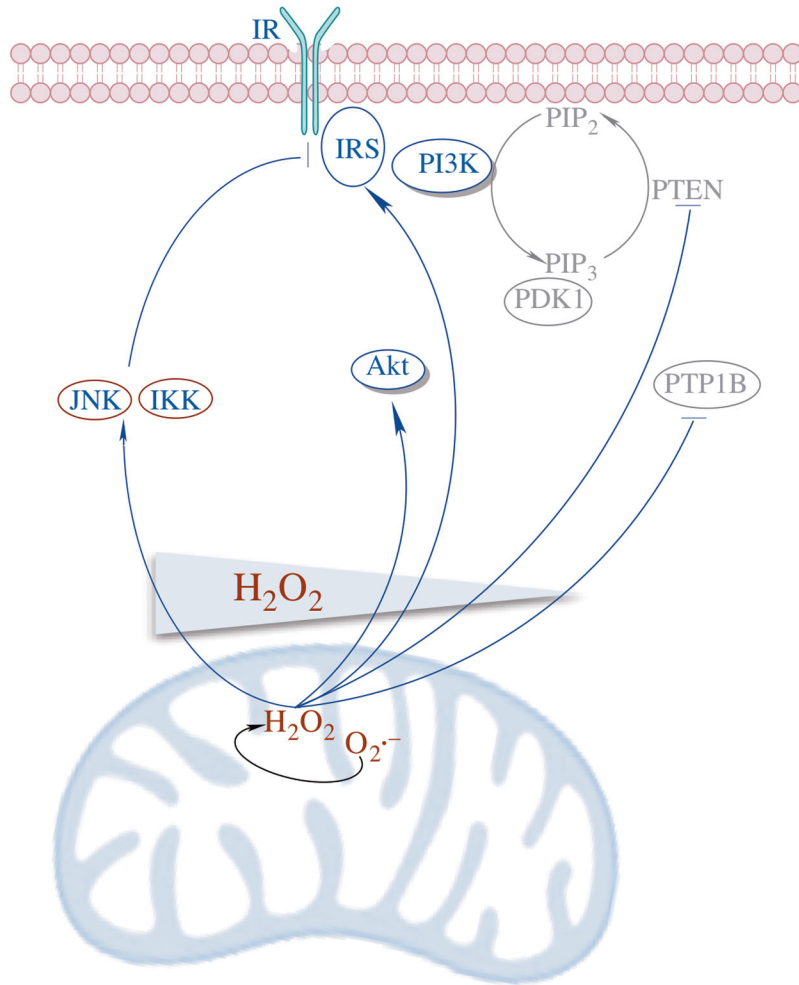
Fig. 4. H$_2$O$_2$ modulates IIS in a concentration-dependent manner

Lower concentration of H$_2$O$_2$ activates IIS via (a) oxidation and activation of insulin receptor, (b) oxidation and inhibition of phosphatases that negative regulate IIS including PTP1B and PTEN, and (c) activation of Akt. Conversely, higher levels of H$_2$O$_2$ inactivate IIS due to the stimulation of inhibitory pathways of IIS such as JNK and IKK.
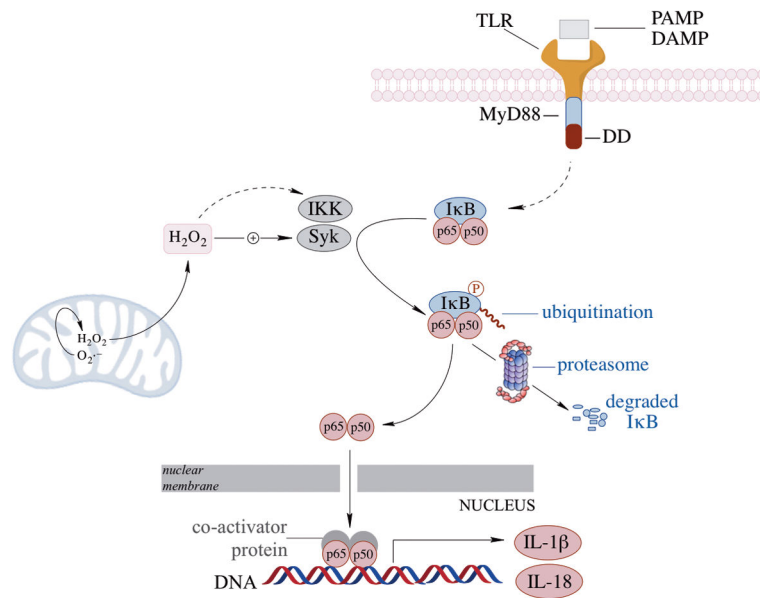
Fig. 5. NFκB signaling in the inflammatory response

NFκB activation, and subsequent translocation to the nucleus can be initiated by different PAMPs or DAMPs via the toll-like receptors (*e.g.,* TLR4). Mitochondrial H_2O_2 can facilitate NFκB activation by modulating the redox sensitive Syk and IKK pathways which phosphorylate the inhibitory protein IκB and lead to IκB ubiquitination and degradation, thereby releasing NFκB and its translocation to the nucleus.
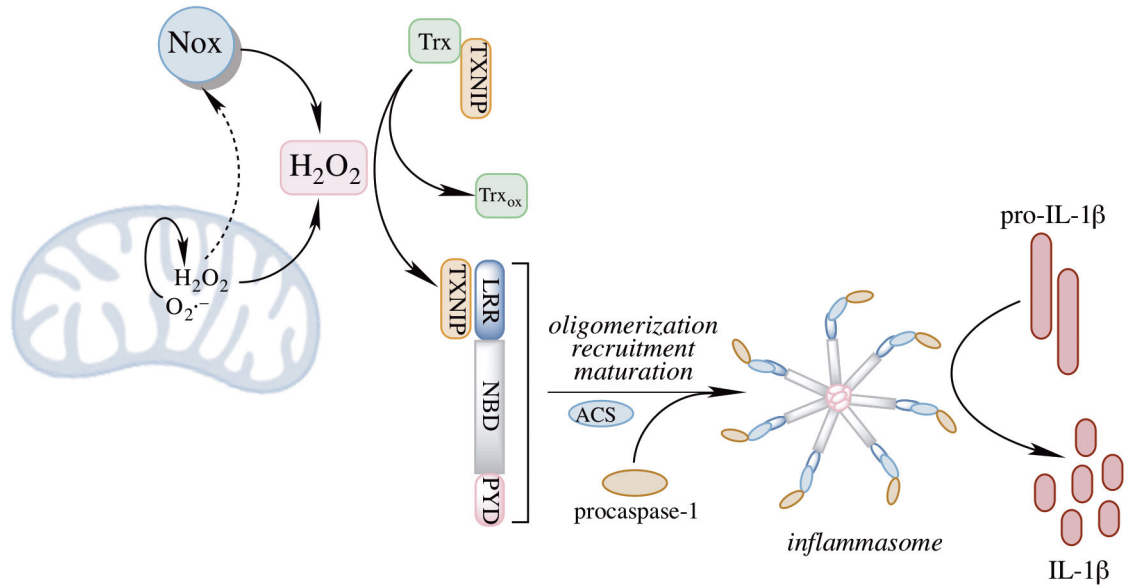
Fig. 6. Mitochondrion-driven activation of the NLRP3 inflammasome

H_2O_2 generated by mitochondria and NADPH oxidase (NOX) enzymes are major sources for NLRP3 priming and activation. NOX enzymes are dependent on mitochondrial H_2O_2 for their activation. Once primed, the inflammasome components oligomerize and form a complex with ACS, generating a platform for caspase-1 to catalyze the proteolytic activation of IL1β.
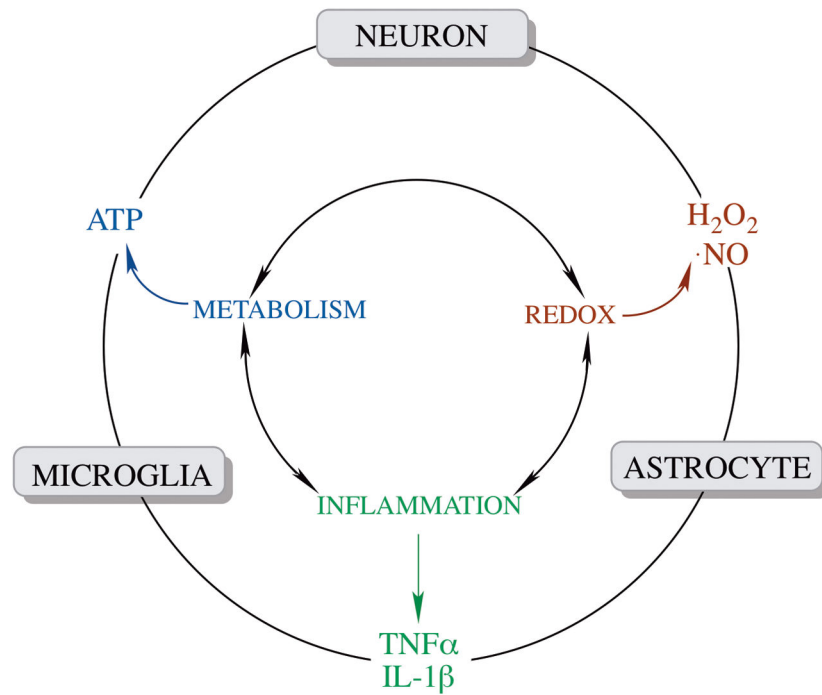
Fig. 7. Coordination of metabolic, redox, and inflammatory signals in brain aging and neurodegeneration

The metabolic-, redox- and inflammatory components are interconnected and signals (metabolic signal: ATP; redox signal: H_2O_2 and NO; inflammatory signal: cytokines) originated from each component are involved in intra- (inner circle) and inter- (outer circle) cellular communications in the brain.