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Review article

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. Interaction of these systems is reviewed based on basic research and clinical studies.

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 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].

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.

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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].

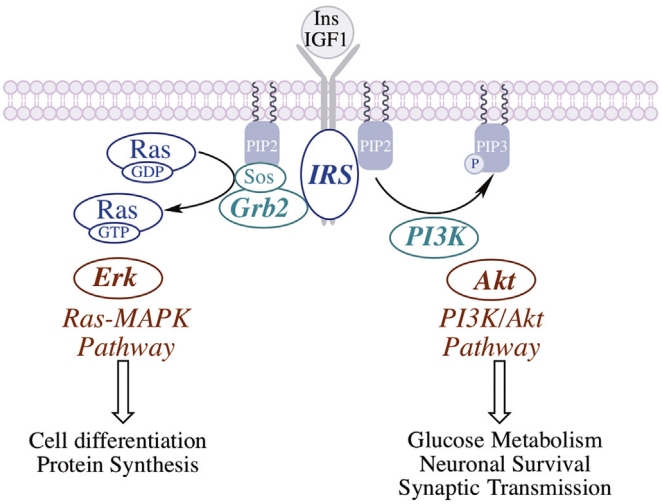

Fig. 1. Insulin/IGF1 signaling (IIS) is primarily orchestrated through insulin and IGF1 and the PI3K/Akt and ERK1/2 signaling pathways. Binding of the ligand to insulin receptor or IGF1 receptor activates the insulin receptor substrate (IRS). Binding of PI3K to the phosphorylated IRS activates the PI3K/Akt 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.

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