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Review

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and Alzheimer's disease

Glycéraldéhyde-3-phosphate déhydrogénase (GAPDH) et la maladie d'Alzheimer

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ABSTRACT

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is a ubiquitous enzyme that catalyzes the sixth step of glycolysis and thus, serves to break down glucose for energy production. Beyond the traditional aerobic metabolism of glucose, recent studies have highlighted additional roles played by GAPDH in non-metabolic processes, such as control of gene expression and redox post-translational modifications. Neuroproteomics have revealed high affinity interactions between GAPDH and Alzheimer's disease-associated proteins, including the β-amyloid, β-amyloid precursor protein and tau. This neuronal protein interaction may lead to impairment of the GAPDH glycolytic function in Alzheimer's disease and may be a forerunner of its participation in apoptosis. The present review examines the crucial implication of GAPDH in neurodegenerative processes and clarifies its role in apoptotic cell death.

Mots clés :
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RÉSUMÉ

La glycéraldéhyde-3-phosphate déshydrogénase (GAPDH) est une enzyme ubiquitaire qui catalyse la sixième étape de la glycolyse et sert à briser le glucose pour la production d'énergie. Au-delà du métabolisme aérobie traditionnel du glucose, des études récentes ont mis en évidence les rôles joués par la GAPDH dans les processus non-métaboliques tels que le contrôle de l'expression génique et les modifications post-traductionnelles redox. La neuroprotéomique a révélé des interactions de haute affinité entre la GAPDH et les protéines associées à la maladie d'Alzheimer, y compris le β-amyloïde, le précurseur de β-amyloïde et la protéine tau. Son interaction avec des protéines neuronales peut conduire à la perte de la fonction glycolytique de la GAPDH dans la maladie d'Alzheimer et peut être un précurseur de sa participation dans les processus apoptotiques. La présente revue examine l'implication cruciale de la GAPDH dans les processus neurodégénératifs et clarifie son rôle dans l'apoptose.

1. Introduction

Alzheimer disease (AD) is a severe neurodegenerative disease affecting the elderly and together with its related syndromes (e.g. frontotemporal dementia, dementia associated with cerebrovascular disease and Lewy body dementia) are the leading causes of dementia [1]. Over a century ago, Alois Alzheimer described typical clinical characteristics, which are renowned neuropathological hallmarks of AD: progressive impairment of episodic memory and instrumental signs, histological examination of miliary bodies (senile plaques – composed of extracellular deposits of β-amyloid (Aβ)) and dense bundles of fibrils

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(neurofibrillary tangles inside nerve cell bodies – composed of hyperphosphorylated tau) [2–4]. Synaptic loss, dendritic retraction, neuronal progressive loss, dystrophic neuritis, granulovacuolar degeneration, neuropil threads, Hirano bodies, and cerebrovascular amyloid are also typical characteristics that are thought to have critical influence on cognitive and memory impairments observed in AD patients [5–9]. At this time, accurate early diagnosis of AD is problematic because early neurological symptoms of relentless neurologic deterioration are shared by a variety of disorders, and definitive diagnosis is only possible based on histological investigation of the brain at autopsy.

Analysis of the human proteome has made significant advances and there has been a growing interest in applying proteomics to research clinical diagnostics and predictive therapies of neurodegenerative disorders [10]. Identification and determination of proteins affecting the degree of neurodegeneration could contribute to the development of protein biomarkers that are critical for diagnosing and monitoring the disease and its progression, as well as predicting and monitoring the clinical benefits of the response to treatment. In addition, identification of such proteins has greatly facilitated studies at revealing the molecular events underlying neurodegenerative diseases. Research conducted in recent years has revealed the involvement of the oxidoreductase, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), in AD pathology [11–13]. Genetics and neuroproteomics have revealed high affinity interactions between GAPDH and neurodegenerative disease-associated proteins, including the β-amyloid (Aβ) precursor protein (AβPP), Aβ and neurofibrillary tangles. GAPDH is subject to several forms of oxidative modifications in brains of AD patients, which fundamentally disturb its chemical structure and biological function, including S-glutathionylation, S-nitrosylation, and its reaction with reactive oxygen species (ROS) [14–17]. Here, we review the essential role of GAPDH in Alzheimer's disease pathology; we particularly focus on its structural modifications that induce amyloid and tau proteins aggregation.

2. GAPDH structure and function

GAPDH enzymes are a family of largely expressed oxidoreductases known for their key role in glycolysis. In glucose metabolism, it is catalyzing the phosphorylation of glyceraldehyde-3-phosphate (G3P) to 1,3-bisphosphoglycerate using nicotinamide adenine dinucleotide (NAD^+) as a cofactor. It provides the biological starting point not only for the glycolytic synthesis of ATP but also for reducing equivalents accessible for oxidative phosphorylation. GAPDH exists as a homologous tetramer (~148 kDa), dimer (~74 kDa) and monomer (~37 kDa) [18]. Each GAPDH monomeric form consists of two conserved binding domains: an N-terminal NAD^+-binding domain and a C-terminal catalytic, or G3P-binding domain [19]. In general, GAPDH is used as a housekeeping gene, or cytosolic control marker in protein and gene expression studies, as well as a reference loading control in routine biochemical analysis (e.g. Northern and Western blots) because of its sequence preservation and expression across species [20]. However, recent experimental evidence suggest that beyond glycolytic functions, GAPDH is in reality a multifunctional protein that has been reported to: bind nucleic acids [21,22], regulate gene expression/transcription [23], possess kinase/phosphotransferase activity [24], facilitate vesicular transport [25], and bind integral membrane ion pumps associated with cell Ca^{2+} release [26], as well as interact with a number of small key molecules, including ribozymes [27], glutathione (GSH) [28], p53 [29], and nitric oxide (NO) [30–33]. Moreover, GAPDH also interacts and form complexes with neurodegenerative disease-related proteins, like huntingtin [33,34], β-amyloid and the β-amyloid precursor protein (AβPP) [35–38]. Hence, GAPDH cellular manifestations independent of its role in energy production is of great importance to neurodegenerative disease research, specifically in brains of subjects with AD because formation of β-APP or β-AP–GAPDH protein complexes could result in a reduced level of glycolysis and thus of glucose consumption.

3. GAPDH and β-amyloid/β-amyloid precursor protein aggregation

As indicated, recent studies revealed the specific interaction of GAPDH with neurodegenerative disease proteins and this could potentially correlate with pathological features. Initial investigations into the involvement of GAPDH in AD reported cross-reactivity between GAPDH and the monoclonal antibody Am-3, which recognizes parent AβPP but not cleaved Aβ, in brain specimens from AD patients [12]. Tamaoka et al. suggested that such cross-reactivity was unlikely ascribed to homologies between epitopes involving similar post-translational modification, since their putative sites are presumed to lie outside the Aβ (1–42) sequence region in AβPP, but were most likely due to conformational similarities between Aβ and GAPDH, which would ultimately complicate the immunochemical and immunocytochemical detection of AD [39,40]. Furthermore, a direct interaction between GAPDH and AβPP has been observed by gel filtration by Schulze et al., in which brain monomeric GAPDH interacted with the cytoplasmic C-terminal domain of recombinant AβPP, while maintaining the rate of glycolysis [15]. Subsequent studies established that brain-derived GAPDH could bind a variety of Aβ isoforms, exhibiting greatest affinity for Aβ (1–42) [41–43].

Recently, antibodies that reveal Alzheimer's disease plaques were shown to also interact with nuclear GAPDH from post-mortem specimens obtained from AD subjects and from cultured cells incurring apoptosis. Mazzola et al. reported decreased intracellular glycolytic activity of GAPDH in AD patients, which was 27% less glycolytically active in Alzheimer's cells as compared with age-matched controls, in both nuclear and post-nuclear fractions [44]. These results provided critical evidence that inhibition of GAPDH's enzymatic activity in AD cells is due to post-translational alterations of the GAPDH protein structure and witnessed that subcellular fractionation analysis may be vital to understanding GAPDH's cellular function in neurodegenerative diseases.

As mentioned earlier, GAPDH can undergo many different oxidative post-translational modifications, which influence its chemical structure and biological activity, and are able to form highly stable complexes with soluble Aβ to form aggregates. Active site modifications consist of mono-ADP-ribosylation, GAPDH-transition metal complex formation, S-glutathionylation and S-nitrosylation by NO or other reactive nitrogen species [45,46]. In brains of AD individuals, such oxidative protein modifications are common, as several groups reported the relationship between oxidative stress and damage as a major hallmark of AD pathology, precipitating loss of neurons, synapses, and in the long run, normal brain function. Cumming et al. revealed that Aβ promotes an increase in GAPDH intermolecular disulfide bonding in all examined brain extracts from AD individuals as compared with age-matched controls [36]. In fact in their study, Aβ treatment of primary and immortalized neurons resulted in the loss of a 120 kDa disulfide-linked isoform of GAPDH in the cytosol and concomitant appearance of the same isoform in the nucleus, suggesting that oxidative stress induced by Aβ promotes nuclear accumulation of disulfide-bonded GAPDH. In addition, Aβ treatment increases the intracellular concentration of ROS in cultured nerve cells. Disulfide-linked insoluble aggregates of high molecular weight GAPDH found in AD patients, and aged transgenic AD

mice may increase cytotoxicity and indirectly trigger apoptosis. Moreover, treatment of HT22 cells with H_2O_2 or diamide mimicked the formation of high molecular weight disulfide-linked GAPDH multimers and resulted in a reduction of about 94% and 66%, respectively, of the GAPDH glycolytic activity as compared to untreated cells. To investigated the molecular mechanism that underlies oxidative stress-triggered aggregation of GAPDH and the relationship between structural abnormalities in GAPDH and cell death, Nakajima et al., prepared cysteine-substituted mutants C149S, C153S, C244A, C281S, and C149S/C281S of GAPDH to identify residues responsible for disulfide-linked aggregates formation [47]. Their results revealed that neither C149S nor C149S/C281S mutants aggregated, proposing that the active site cysteine of GAPDH plays an essential role in amyloid binding, aggregation and promotion of cell death. Hence, post-translational modifications of the redox-sensitive glycolytic enzyme, GAPDH, induces amyloid-like aggregation through alteration in GAPDH's conformation via formation of aberrant disulfide bonds at the active site at cysteine 149, which leads to the formation of insoluble aggregates thereby promoting neuronal apoptosis.

4. GAPDH and tau aggregation

Neurofibrillary tangles (NFTs) are intraneuronal lesions formed by hyperphosphorylation of the microtubule-associated protein tau that leads to insoluble neurotoxic aggregates, of which, paired helical filaments (PHF)-tau are a major component. Generally, tau binds to microtubules and is essential for axonal transport and maintenance of the neuronal network. Neurodegenerative tauopathies suggest that the abnormal hyperphosphorylation of the tau protein results in a loss of its function, which leads to depolymerization of microtubules, formation of neurotoxic NFTs and disturbed axonal transport, followed by neuronal dysfunction and neurodegeneration [48–50]. The explicit relation between Aβ deposition and tau-related pathology is not clear yet, but tau aggregation has many consequences on neurons and is probably the final common cause of neurodegeneration in AD. LC-MS/MS analysis confirmed that GAPDH co-localized with NFTs and immunoprecipitated with PHF-tau in specimens from the temporal cortex of brains from AD patients [51,52]. Further studies by Chen et al. provided evidence that tau was able to interact and induce the denaturation and inactivation of GAPDH. Authors have also established that the phosphorylated and pre-aggregated PHF-tau was unable to bind or affect GAPDH denaturation or activity, suggesting a direct involvement of GAPDH in tau aggregation and NFT formation in AD patients' brains.

5. Conclusion

Considerable progress in the search of a novel AD biological biomarker has been made with markers derived from pathological lesions. To date, the most promising sources of biomarkers in AD were cerebrospinal fluid (CSF) and blood plasma, because of their accessibility. Several biomarkers have been suggested such as the CSF total-tau [53], phospho-tau levels and CSF Aβ (1–42) levels [54,55]. The identification of proteins affecting the degree of neurodegeneration could enormously contribute to the development of biomarkers and may be explored for their value as a new drug targets in AD. The strong evidence of the interaction between GAPDH and AβPP, Aβ, and tau demonstrates its direct participation in the aggregation of these three proteins into their insoluble counterparts. Although the precise molecular mechanisms of many of the GAPDH interactions and processes described in this review are not yet clear, the structure, activity and subcellular localization of GAPDH remains crucial for understanding the countless roles it plays in normal and neuropathological cellular functions. Therefore, these findings open new avenues for diagnosis by using GAPDH as a biomarker and a promising therapeutic target to slow or cure neurodegeneration in brains of AD patients.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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