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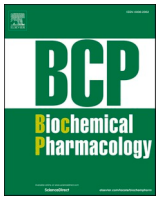

Review

A strategic tool to improve the study of molecular determinants of Alzheimer's disease: The role of glyceraldehyde

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ABSTRACT

Alzheimer's disease (AD) is the most prevalent form of dementia and is characterized by progressive neurodegeneration leading to severe cognitive, memory, and behavioral impairments. The onset of AD involves a complex interplay among various factors, including age, genetics, chronic inflammation, and impaired energy metabolism. Despite significant efforts, there are currently no effective therapies capable of modifying the course of AD, likely owing to an excessive focus on the amyloid hypothesis and a limited consideration of other intracellular pathways. In the present review, we emphasize the emerging concept of AD as a metabolic disease, where alterations in energy metabolism play a critical role in its development and progression. Notably, glucose metabolism impairment is associated with mitochondrial dysfunction, oxidative stress, Ca^{2+} dyshomeostasis, and protein misfolding, forming interconnected processes that perpetuate a detrimental self-feeding loop sustaining AD progression. Advanced glycation end products (AGEs), neurotoxic compounds that accumulate in AD, are considered an important consequence of glucose metabolism disruption, and glyceraldehyde (GA), a glycolytic intermediate, is a key contributor to AGEs formation in both neurons and astrocytes. Exploring the impact of GA-induced glucose metabolism impairment opens up exciting possibilities for creating an easy-to-handle in vitro model that recapitulates the early stage of the disease. This model holds great potential for advancing the development of novel therapeutics targeting various intracellular pathways implicated in AD pathogenesis.

In conclusion, looking beyond the conventional amyloid hypothesis could lead researchers to discover promising targets for intervention, offering the possibility of addressing the existing medical gaps in AD treatment.

1. Introduction

Alzheimer's disease (AD) is the most common form of dementia and is characterized by chronic and progressive neurodegeneration resulting in severe cognitive, memory, and behavioral impairment [1]. According to the World Health Organization, dementia affects approximately 55 million people worldwide, with 60–80% of patients having an AD diagnosis [2]. More than 95% of AD cases appear to be sporadic with a later age of onset (60 to 65 years) and are characterized by complex genetic and environmental interactions [3]. The early onset or familial form accounts for less than 5% of the AD population, and it mainly arises from mutations in three genes: amyloid precursor protein, presenilin 1 and presenilin 2 [4]. The two cardinal features of AD are senile plaques, which are mostly composed of β-amyloid (Aβ) protein accumulation,

Abbreviations: Aβ, β-amyloid; AD, Alzheimer's disease; AGEs, Advanced Glycation End products; AMPK, Monophosphate Activated Protein Kinase; GA, Glyceraldehyde; GAPDH, Glyceraldehyde-3 Phosphate Dehydrogenase; GLP-1, Glucagon Like Peptide 1; GLUT, Glucose Transporters; mTOR, Mammalian Target of Rapamycin; RAGE, Advanced Glycation End-products Receptor; ROS, Reactive Oxygen Species; SOD, Superoxide Dismutase.

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and neurofibrillary tangles, which predominantly consist of the hyperphosphorylated form of tau protein [5]. AD is also accompanied by a loss of neuronal population, synapse degeneration, proliferation of reactive astrocytes, alteration of the glial phenotype [6], and oxidative damage of microglia [7]. These AD-related brain changes result from a complex interplay that involves several factors, including age, genetics, chronic inflammation, and energy metabolism impairment [8]. This evidence lends support to the multifactorial hypothesis of AD and emphasizes the concomitant action of multiple players, making it more difficult to identify a single druggable target. Indeed, although large efforts have been made to pursue this objective, there are currently no disease-modifying therapies [9], and AD treatment remains one of the main unmet medical needs. This may also be because the majority of the research has been centered on finding effective therapeutics for AD focused on the Aβ hypothesis, while it could be of greater impact to address multiple intracellular pathways in a more comprehensive way. In this light, studying AD as a metabolic disease is particularly attractive because the metabolic impairment that characterizes AD may be the source of several alterations that converge on the pathogenesis and progression of the disease [10]. Glucose dysmetabolism is increasingly emerging as a mediator of mitochondrial dysfunction, oxidative stress and protein misfolding [11], which could be considered mechanistic links among AD and targets for therapeutics since they are interrelated in sustaining disease progression through a negative self-feeding loop [12]. Notably, in this framework, the excess of free sugars has been shown to accelerate the production of advanced glycation end products (AGEs), which are neurotoxic compounds, the levels of which are significantly increased in AD [13]. The glycolytic intermediate glyceraldehyde (GA) is considered one of the main promoters of AGEs formation [14] in both neurons and astrocytes [15,16].

In this review, we focus on the alteration of cell metabolism, highlighting its impact on AD pathogenesis and progression. We also describe how strategies that impair glucose metabolism could be used to create an easy-to-handle in vitro model that recapitulates the early stage of the disease.

2. Brain energy metabolism: from physiology to pathology

It is well known that the brain consumes the greatest amount of energy of all the organs in the body to sustain proper neuronal functions [8,17,18]. This massive energy demand predisposes neurons to be extremely intolerant to inadequate supply, and its disturbance leads to a variety of diseases. Therefore, brain physiology and function are tightly dependent on glucose, and alterations at different key points of glucose import and metabolism can negatively impact processes such as memory and cognition, predisposing or accelerating neurodegeneration.

Brain needs and different cell types can influence glucose metabolization, which is mainly represented by the following pathways: (1) glucose can be converted to pyruvate or lactate by glycolysis and then undergoes oxidative phosphorylation; (2) it can be used to produce glycogen by glycogenesis, which allows the formation of an energy deposit in astrocytes; or (3) it can generate 5-carbon sugars and nicotinamide adenine dinucleotide phosphate (NAPDH) through the pentose phosphate pathway, which may confer protection against oxidative stress [19]. Furthermore, glucose metabolism provides substrates for the synthesis of neurotransmitters and operates on cell survival control by glucose metabolizing enzymes, in addition to meeting the energy needs essential for neurotransmission [20].

Neurovascular coupling regulates glucose supply and its distribution to brain cells across a highly efficient metabolic network. By positron emission tomography and single-photon emission computed tomography, it has been observed that AD patients show characteristic patterns of hypoperfusion and hypometabolism in the parietotemporal-associated neocortical areas that correlate with senile plaques, neurofibrillary tangles, vascular amyloid deposits, and neuronal cell loss [21,22]. The reduction in cerebral blood flow leads the neural tissue to become hypoxic and presumably contributes to the decrease in glucose metabolism, primarily impacting the onset of the disease. The progressive decline in the cerebral metabolic rate of glucose consumption in the entorhinal cortex and parietal lobes appears before the advent of AD clinical symptoms, which the subsequent pathology confirms [23]. Thus, blood flow changes seem to start early in preclinical AD, with a decrease in metabolism [24,25].

The hydrophilic nature of glucose implies its transport across the cell membranes by carrier proteins. Three gene families are involved in the synthesis of proteins called “glucose transporters”: *SLC2A*, *SLC5A* and *SLC50A* [26]. The sodium-independent glucose transporters (GLUT proteins, *SLC2A* genes) are integral membrane uniporters that transport a single water molecule across its gradient and may not use energy. GLUT1 and GLUT3 are the major glucose transporters in the brain. GLUT1 is expressed by astrocytes and endothelial cells [27]. GLUT3 is located in neurons, especially in neurites, dendrites and soma [28]. A decrease in GLUT1 and GLUT3 expression has been detected in AD patients [29–32]. The decrease in glucose transporters negatively impacts glucose uptake and abundantly influences AD pathophysiology involving glucose metabolism.

Recent studies have confirmed damage to glycolytic flux by ^{18}F-fluorodeoxyglucose positron emission tomography [33] and fluorescence lifetime imaging microscopy [34].

Analysis of cerebrospinal fluid by ^{18}F-Fluorodeoxyglucose Positron Emission Tomography in amyloid-positive patients with mild cognitive impairment and dementia revealed a left lateralized decline in the regional cerebral glucose metabolic rate. In support of this evidence, alterations in the activity of glycolytic enzymes, glucose consumption and amino acid metabolism were detected in AD postmortem brains by several groups [35–37]. Furthermore, Liang et al [38] showed a downregulation of several genes involved in energy metabolism in AD patients and a mouse model of the pathology. The evidence that symptomatology never occurs without glucose hypometabolism, and that the severity of clinical symptoms is strongly correlated with the extent of the metabolic changes further highlights the key role played by energy metabolism in AD [39,40]. Changes in glycolytic pathways emerged as early hallmarks of AD and can promote Aβ deposition and Tau protein phosphorylation [41]. Specifically, a reduction in the expression of glucose-6-phosphate isomerase, phosphofructokinase, aldolase, phosphoglycerate mutase, lactate dehydrogenase [42] and pyruvate dehydrogenase complex [43] was detected in AD-affected brains, while primary neurons isolated from transgenic AD mice showed a decrease in mitochondrial and cytosolic NAD(P)H by Fluorescence Lifetime Imaging Microscopy, indicating damage to glycolytic flux [34].

3. The role of AGEs (GA-AGEs) in AD

GA is one of the most potent precursors of AGEs, as it causes nonenzymatic glycation of proteins, resulting in irreversible toxic AGEs [44]. In healthy individuals, GA is converted to glyceraldehyde 3-phosphate by glyceraldehyde-3 phosphate dehydrogenase (GAPDH), and it is maintained at low levels [45]. Needham and colleagues reported that in neurons, GA reduces the activity of GAPDH, which in turn stimulates an increase in GA-AGEs, suggesting a feed-forward mechanism [46]. In the AD brain, the GAPDH enzyme can undergo significant modifications (e.g., oxidative and posttranslational), which can affect its structure and activity [47–49]. Therefore, altered regulation of the glycolytic pathway may elicit an increase in GA levels and the accumulation of GA-derived AGEs, resulting in cytotoxicity [44,50] (Fig. 1). The pathological effects of AGEs are mainly mediated by multiple mechanisms, including their ability to produce reactive oxygen (ROS) and nitrogen species, as well as inflammation, triggering aberrant protein glycation, abnormal protein folding, aggregation of irregular or oligomeric proteins, cellular dysfunction, and upregulation of apoptotic signaling pathways [51]. AGEs actions are mediated by their binding to

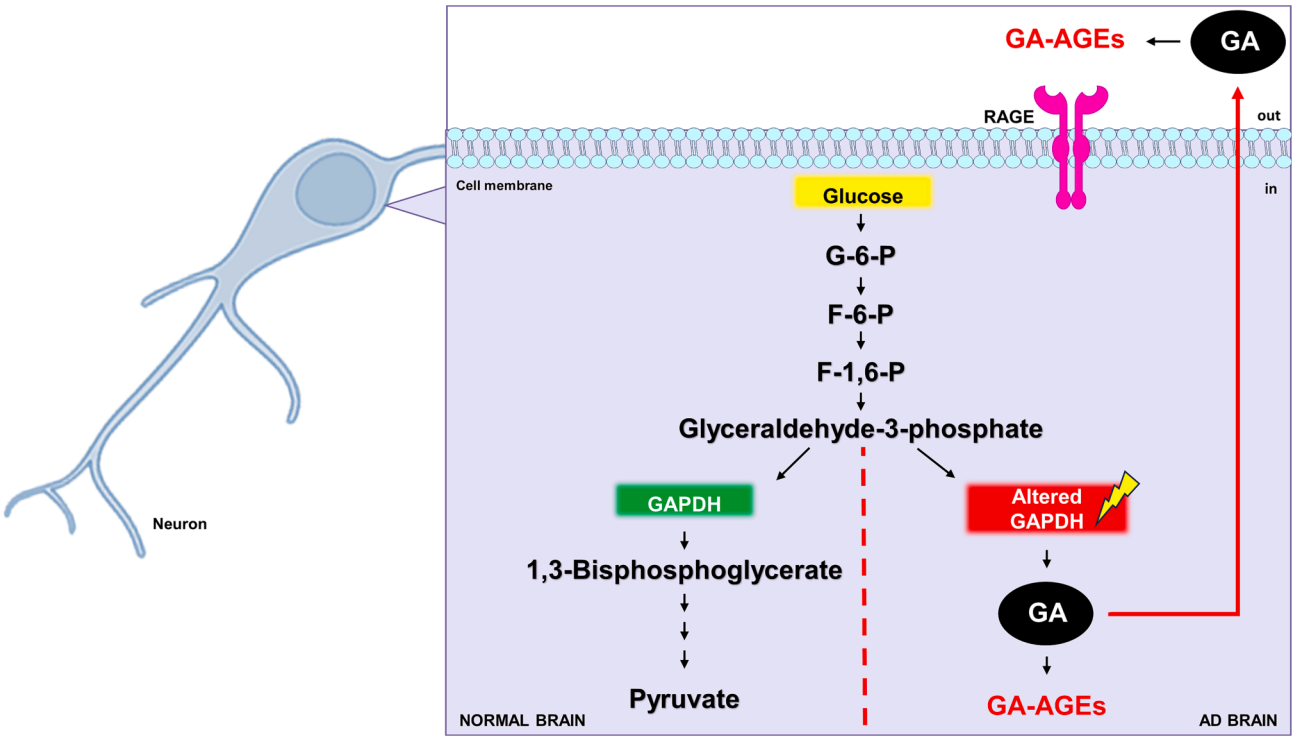

Fig. 1. A schematic representation of the glycolytic pathway and GA-AGEs production in AD brain. In healthy individuals, the glycolytic enzyme GAPDH converts glyceraldehyde-3-phosphate in 1,3-bisphosphoglycerate efficiently, forming pyruvate. In AD brain, GAPDH activity is compromised and leads to an increase in GA-AGEs due to the conversion of glyceraldehyde-3-phosphate in GA, suggesting a feed-forward mechanism. The interaction between RAGE and GA-AGEs in AD brain can trigger a cascade of cellular responses, potentially contributing to neuroinflammation and neuronal damage. G-6-P: glucose-6-phosphate; F-6-P: fructose-6-phosphate; F-1,6-P: fructose-1,6-bisphosphate.

the receptor for advanced glycation end-products (RAGE), a member of the immunoglobulin superfamily of cell surface molecules [52]. In the normal human brain, the expression of RAGE has been detected in neurons, microglial cells, and astrocytes [53]. Interestingly, RAGE expression has been reported to be significantly upregulated in neurons closely related to neuritic plaques and in the vasculature of the AD-affected brain [54]. Different studies have provided evidence that the signaling pathway mediated by RAGE/AGEs interactions may drive inflammatory processes and mediate ROS generation, triggering the pathophysiological processes that characterize the early stage of AD [55,56].

The first evidence of AGEs involvement in AD comes from the finding of a 3-fold increase in AGEs in plaques from AD patients compared to healthy individuals [57] and from the evidence that AGEs contribute to both Aβ and oligomerization [58]. Later, several studies provided evidence supporting the correlation between AGEs and the development of neurodegenerative processes in AD [59–61]. In particular, a growing body of evidence supports the hypothesis that the neurotoxic effects of AGEs may rely on their ability to regulate Aβ aggregation and its accumulation, and the glycation process seems to further intensify the toxicity of Aβ oligomers [50,62–64]. The neurotoxic effects of AGEs also contribute to Tau protein hyperphosphorylation, most likely through the activation of glycogen synthase kinase-3 mediated by RAGE, leading to synapse damage and memory deficits [63]. Of note, the detection of glycated protein and AGEs in the serum and cerebrospinal fluid of AD patients reinforced the hypothesis that the glycation of Aβ could be a mechanism involved in the risk of developing AD [64,65]. The complex involvement of the RAGE system in this pathology is underlined by the extensive involvement of the glucose metabolic pathway at different levels. For example, emerging data indicate that the peptide hormone and growth factor glucagon-like peptide 1 (GLP-1), which plays a physiological signaling role in regulating cell metabolism and energy utilization [66], exerts a neuroprotective role in neurodegenerative disorders, including AD, through its ability to promote neurogenesis and ameliorate cognitive performance [67–69]. For instance, in AGE-stressed neurons, the effect of GLP-1, mediated by GLP-1 receptor, positively affects neuronal viability and functionality by anti-inflammatory and antioxidant mechanisms, restoring the loss of mitochondrial membrane potential and DNA oxidation and reducing Aβ accumulation and Tau hyperphosphorylation [70–72]. In addition, Chen and coworkers reported that GLP-1 reduced the cell apoptosis induced by AGEs in SH-SY5Y cells [73], suggesting that GLP-1 agonists, through their abilities to cross the blood–brain barrier, could improve both cognitive and memory functions and protect against brain damage.

4. The GA in vitro model

In line with the multiple findings highlighting a key role of AGEs in AD development and progression, it has been observed that exposure to GA in SH-SY5Y neuroblastoma cells causes an increase in AGEs, triggering the dysregulation of AD biomarker levels and ultimately cell death [74]. Starting from this finding, we recently established an in vitro model based on the challenge with GA to reproduce the main molecular changes that accompany AD genesis and progression [75–77]. First, we conducted experiments aimed at testing the effect of GA on retinoic acid-differentiated SH-SY5Y cells, and second, we tried to confirm the obtained results in primary rat cortical neurons. The glucose metabolism impairment induced by GA causes a concentration- and time-dependent cell injury that is accompanied by the alteration of the specific AD biomarkers $A\beta_{1\text{-}42}$ and hyperphosphorylated Tau [75–77]. The rise in $A\beta_{1\text{-}42}$ accumulation could be explained hypothesizing a compromised processing of amyloid precursor protein, which could be forced toward the formation of toxic amyloidogenic fragments during metabolic impairment [78–80] (Fig. 2). It is intriguing to observe that in cells subjected to GA, there is a pronounced deposition of Aβ within mitochondria [77], highlighting a dysfunctional interplay between the

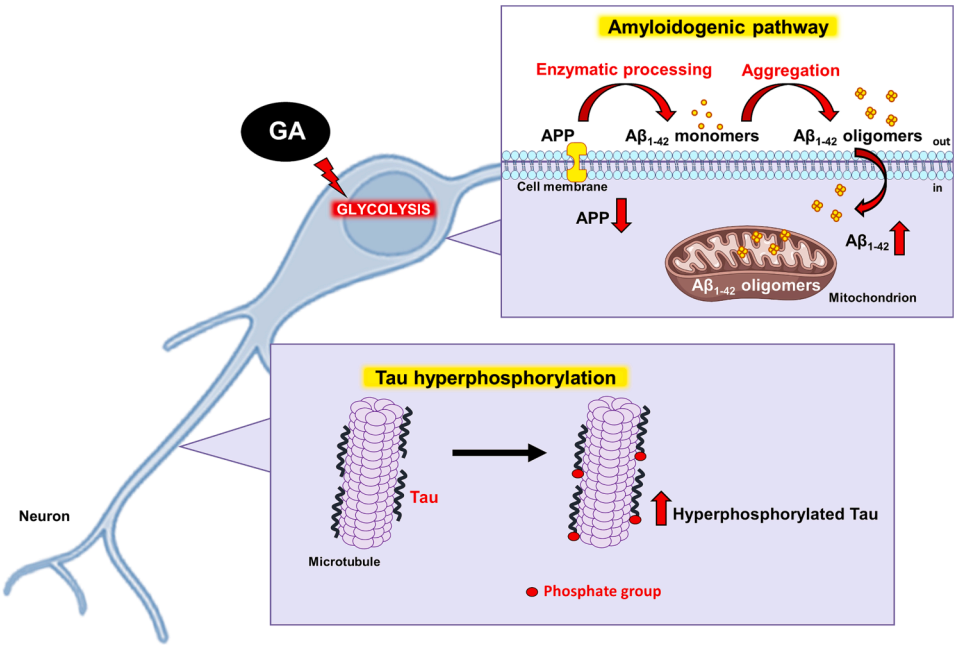

Fig. 2. Schematic representation illustrating the key neuropathological features of AD induced by GA. During metabolic impairment APP may undergo enzymatic processing, resulting in Aβ monomers production. These monomers can aggregate into $A\beta_{1\text{-}42}$ oligomers, which subsequently may accumulate within mitochondria. The formation of toxic amyloidogenic fragments is accompanied by the alterations in the conformation of Tau protein, leading to an increased phosphorylation, resulting in Tau hyperphosphorylation, and, consequently, in a reduced affinity for microtubules and subsequent microtubule instability.

neurotoxic Aβ oligomers and alterations of mitochondrial functions. Accordingly, growing evidence indicates that amyloid precursor protein and Aβ have the ability to enter mitochondria, where they can interact with different mitochondrial components, resulting in the impairment of ATP synthesis and the simultaneous promotion of ROS accumulation and oxidative stress [81–83]. Based on this finding, we further tested the metabolic changes induced by GA. By monitoring mitochondrial respiration, assessed by cellular oxygen consumption rates, and glycolysis, measured as extracellular acidification rates, we observed that GA negatively affects the overall cellular bioenergetics [76]. In particular, a dramatic decline in both mitochondrial respiration and glycolysis can be observed, in line with the inhibitory role of GA [76]. This analysis revealed further details on the overall mitochondrial performance, the impairment of which is mirrored by the disruption of the mitochondrial membrane potential and the changes in proton leak, both of which are extremely affected by GA treatment [76].

Overall, these findings define a framework characterized by a significant metabolic decline; although it is difficult to identify the cause and the effect, this model allows us to define a cascade of events culminating in detrimental mitochondrial instability. The metabolic dysfunction associated with GA cytotoxicity led us to hypothesize that the perturbation of the oxidative cell status may also have a role in defining GA-induced damage. This hypothesis was confirmed by the finding that GA exposure induces an overproduction of both intracellular and mitochondrial ROS [75–77]. Oxidative stress reflects an imbalance between the production of reactive species and the activity of the antioxidant defense systems, which could be affected at different levels under the action of a specific stressor [84]. Superoxide dismutase (SOD) enzymes represent a main front line of defense against the damage mediated by ROS [77,85]. The importance of this antioxidant system has been proven by several studies reporting its activity as an anti-inflammatory agent and a precancerous cell scavenger [86]. More interestingly, SOD perturbation has been found in different models of AD where the impairment of the enzyme activity was accompanied by the elevation of Aβ levels [87–90]. Consistent with the major role of SOD in antioxidant defense, overexpression of mitochondrial SOD in AD transgenic mouse models ameliorates cellular pathology and memory impairments by improving cognitive functions and reducing Aβ plaques [89,91]. Therefore, we wondered whether this system could be affected by GA challenge. Surprisingly, we observed that GA caused a significant reduction in SOD activity, shifting the cellular redox equilibrium to pro-oxidative conditions [77]. It is intriguing to note that the disruption of oxidative status and the alterations of mitochondrial functions caused by GA occurred concomitantly with both cytosolic and mitochondrial Ca^{2+} dyshomeostasis [77]. In this regard, compelling evidence suggests that oxidative status could impact the functioning of various systems responsible for the regulation of Ca^{2+} homeostasis within cells, potentially resulting in the disruption of intracellular Ca^{2+} levels [92]. In line with these observations, we have recently demonstrated a substantial elevation in intracellular Ca^{2+} levels following exposure to GA, which had a simultaneous effect on the equilibrium of Ca^{2+} within mitochondria due to their buffering activity [77]. Consequently, we propose that this phenomenon could act as the catalyst for a series of events that compromise mitochondrial functions, ultimately culminating in neuronal cell death. Furthermore, the increased levels of Ca^{2+} within mitochondria might be responsible for the observed collapse of $\Delta\Psi_m$ and, simultaneously, potentially exacerbate the imbalance between pro-oxidant and antioxidant defenses, thus triggering the generation of mitochondrial ROS [76,77,93]. This finding supports the idea of cellular cross-talk, wherein all the observed pathophysiological alterations interact to ultimately contribute to neurodegeneration.

Considering the complex and multifactorial nature of AD pathology, alterations in cell death signaling pathways typically related to AD were also explored. Previous studies reported the existence of a connection between oxidative stress (including AGEs toxicity), mitochondrial dysfunction and adenosine monophosphate activated protein kinase (AMPK)-mammalian target of rapamycin (mTOR) dysregulation [94]. For instance, a downregulation of AMPK activity has been reported in AD and in aging [95], and it has also been observed in neurons affected by oxidative damage and mitochondrial alterations [96–98]. Notably, a neuroprotective role of AMPK against AGEs-induced cytotoxicity has been observed [99,100]. mTOR plays a significant role in metabolism, protein translation, cell growth, proliferation, and autophagy. Numerous studies on AD pathology report ample evidence pointing out

the association between AD and mTOR signaling [101]. The alteration of mTOR in AD may reflect the altered autophagy that has been directly related to different chronic diseases, including AD [102]. Activated mTOR and PKR kinases in lymphocytes correlate with memory and cognitive decline in AD [102,103]. The p70 ribosomal S6 kinase plays a crucial role in AD pathology by being one of the key downstream components of the mTOR pathway. Its implication in AD is multifaceted and involves the phosphorylation of Tau protein and the regulation of Aβ production [104–106]. Specifically, in AD pathology, a dysfunctional process of autophagy may reduce the clearance of misfolded proteins and protein aggregates, favoring the accumulation of Aβ. In line with this evidence, GA exposure causes a significant reduction in AMPK expression, which in turn reflects mTOR upregulation [77], and consequently, p70 ribosomal S6 kinase levels also increase (unpublished data), lending support to the existence of multiple molecular mechanisms forming a vicious cycle able to drive the neurodegenerative processes leading to AD.

The GA model is easy to manipulate and provides the possibility to test interventions addressing key aspects of AD pathogenesis, such as energy deficit and oxidative stress. These factors have been successfully studied in various experimental settings, leading to the conclusion that antioxidant molecules and alternative energy substrates can address a significant regression of the AD marker level and improve cell viability [75–77].

5. Seeking a different perspective: the astrocytic point of view

In vitro models may also be useful to study the contribution of a specific cell type in driving a disease. In this context, astrocytes are emerging as key determinants in AD by dictating its progression and outcome. Astrocytes play a crucial role in brain metabolism regulation through multiple mechanisms: they (1) act as gatekeepers of glucose uptake, positioning their end feet at the intraparenchymal capillaries; (2) modulate cerebral blood flow by sensing synaptic activity and energy demand; and (3) can protect against an energy crisis as they store glycogen, which can be converted into lactate [107].

Astrocytes are also affected by AD and undergo several modifications. They became reactive, increasing the expression of glial fibrillary acidic protein, vimentin, nestin and synemin and exhibiting morphological hypertrophy characterized by the thickness of processes [108]. Moreover, reactive astrocytes, which are localized near plaques, exhibit abnormal Ca^{2+} dynamics [109,110] that prompt alterations in neuron-glia communication and damage to synaptic transmission and plasticity [111,112]. Furthermore, reactive astrocytes start to synthetize GABA, shifting the excitation-inhibition balance [113].

Astrocytes express RAGE, which may bind several molecules, including Aβ. This binding activates the receptor, which stimulates a proinflammatory state via the NF-κB pathway. Consequently, NF-κB upregulation promotes the expression of inflammatory cytokines that feed neuroinflammation and prolong the activation of RAGE [114]. Indeed, in AD brains, approximately 70%-80% of astrocytes contain RAGE-positive granules [53], but only a few of them have been shown to be weakly stained for GA-AGEs [50,115], which instead colocalize with inducible nitric oxide synthase, suggesting an involvement of oxidative stress in AGEs production in these cells. Moreover, glucose-derived AGEs (less neurotoxic than GA-AGEs) were also detected in astrocytes. These observations suggest that multiple pathways may be involved in the production of AGEs in the brain and that each of them may cause different types of neurotoxicity, all together contributing to brain damage.

6. Conclusions

AD pathology affects millions of people worldwide, and the number of suffering individuals is showing an increasing trend. To generate new therapeutic approaches, it is crucial to improve the understanding of the molecular mechanisms that underlie the disease. To this aim, in vitro models that recapitulate the main features of AD are important tools in this research field, enabling the screening of effective molecules that could either halt or slow neurodegeneration, potentially leading to the development of specific therapies and providing further insights into the molecular mechanisms underlying AD onset and progression. Most commonly, AD in vitro models rely on the exogenous administration of the oligomeric form of $A\beta_{1\text{-}42}$. This approach is certainly very useful for a preliminary screening of selected compounds to test their ability to inhibit the formation of toxic aggregates and all the related deleterious processes. However, this model does not allow us to investigate the causes that determine the formation of Aβ oligomers, the most neurotoxic aggregates, which play a critical role in causing functional neuron death, cognitive damage, and dementia. Accordingly, it is of crucial importance to use reliable and reproducible protocols to induce Aβ oligomerization, a procedure that can be affected by several variables, sometimes related to the nature of Aβ (not always optimal), giving rise to a setting that may vary between the different experimental sessions. From this perspective, the proposed model is characterized by a main advantage: it is based on the alteration of glucose metabolism, one of the main causes of AD pathogenesis. Available data show that this alteration involves the endogenous production of toxic Aβ aggregates, as well as the hyperphosphorylated form of Tau, followed by subsequent downstream events that trigger the disease [116] (Fig. 3).

This approach allows to investigate the causes that lead to the pathology, which can therefore be explored in a wider and more comprehensive way. On the other hand, it should be emphasized that like other in vitro models, the one we propose, in principle, does not consider the contribution of other cell types, such as the surrounding astrocytes. In this view, it is possible to increase its complexity through the incorporation of other cell types (e.g., coculture with astrocytes) to evaluate how defective astrocytes may affect the viability of neighboring neurons. It is widely accepted that astrocytes can influence and shape neuronal functions; recent evidence suggests that most astrocytes in AD patients contain AGEs and RAGE granules [56], suggesting that astrocytes could take part in the degenerative process that involves neurons. In this light, the proposed model could be a useful tool to study the engagement of astrocytes in neuronal degeneration. Further studies will be needed to validate this model under this perspective, which could be of valuable interest to develop new principles and/or identify specific cell types to target for the treatment/prevention of AD.

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CRediT authorship contribution statement

Silvia Piccirillo: Conceptualization, Validation, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Alessandra Preziuso:** Conceptualization, Validation, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Giorgia Cerqueni:** Conceptualization, Validation, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Tiziano Serfilippi:** Validation, Writing – review & editing. **Valentina Terenzi:** Validation, Writing – review & editing. **Antonio Vinciguerra:** Validation, Writing – review & editing. **Salvatore Amoroso:** Conceptualization, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration. **Vincenzo Lariccia:** Conceptualization, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration. **Simona Magi:** Conceptualization, Validation, Investigation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration.

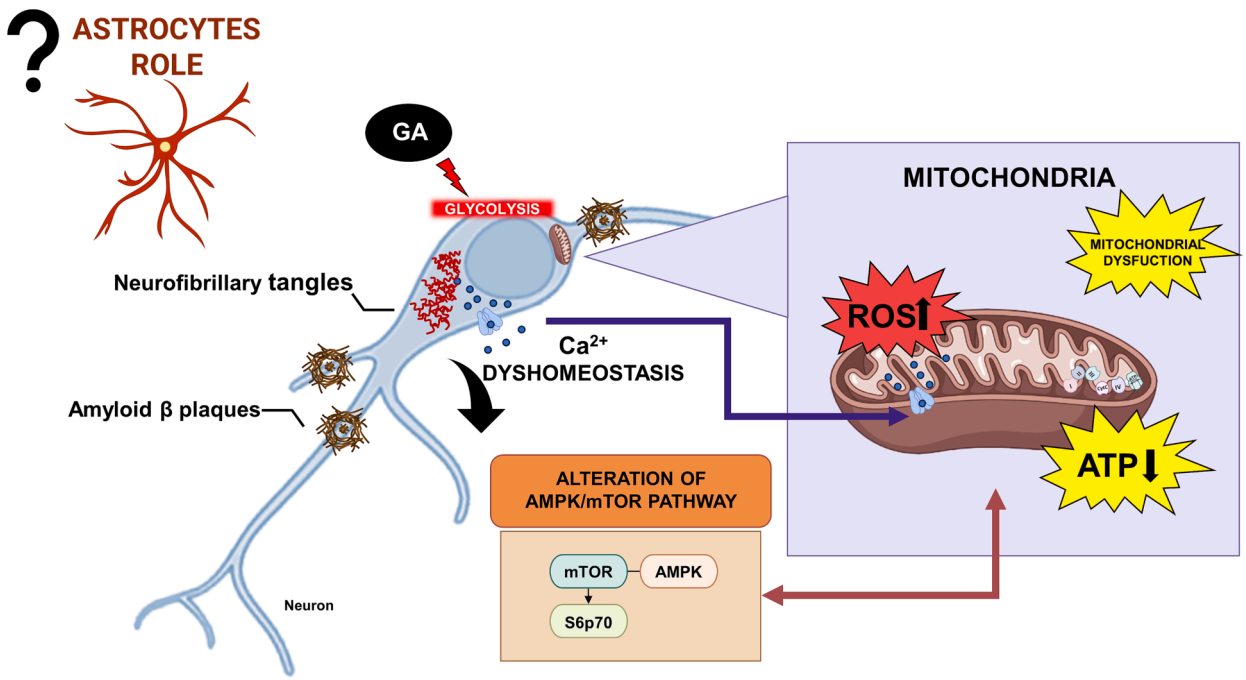

Fig. 3. A schematic depiction of the global effect of GA in neurons. The metabolic impairment generated by GA may represent an upstream event favoring the imbalance between the cellular oxidant species production and the antioxidant capability of the cell, leading to the inactivation of AMPK and the activation of mTOR, thereby triggering a vicious self-feeding cycle culminating in neurodegeneration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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