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Review

Amyloid beta-induced glycogen synthase kinase 3β phosphorylated VDAC1 in Alzheimer's disease: Implications for synaptic dysfunction and neuronal damage

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ABSTRACT

Glycogen synthase kinase 3 (GSK3) is a serine/threonine protein kinase that is involved in the multiple signaling processes of a cell. Increasing evidence suggests that GSK3β plays a key role in multiple cellular processes in the progression of diabetes, obesity, Alzheimer's disease (AD), Parkinson's disease (PD), inflammatory diseases, schizophrenia, bipolar and several mood disorders, and mitochondrial diseases. Recent research has found that increased GSK3β activity is linked to the pathogenesis of AD through amyloid beta (Aβ), phosphorylated tau and mitochondrial dysfunction. Recent research has also revealed that GSK3β is elevated in AD-affected tissues and is critically involved in dissociating the voltage-dependent anion channel 1 (VDAC1) protein from hexokinases, and causing disrupted glucose metabolism, mitochondrial dysfunction and activating apoptotic cell death. The purpose of this article is to review recent research that is elucidating the role of GSK3β in AD pathogenesis. We discuss the involvement of GSK3β in the phosphorylation of VDAC1 and dissociation of VADC1 with hexokinases in AD neurons.

1. Introduction

Alzheimer's disease (AD) is the most common mental illness, characterized by deficits in cognition and memory, as well as changes in personality and behavior [1]. Currently, 5.4 million Americans suffer from AD, and this number is expected to increase as elderly individuals live longer [2]. Histopathological examination of postmortem brains from AD patients revealed that extracellular amyloid beta (Aβ) plaques and intracellular neurofibrillary tangles (NFTs) are the major pathological hallmarks of AD [3]. However, these pathological changes occur late in the disease process, and they are unlikely to represent the primary cause of clinical symptoms. Several other morphological and cellular changes have been identified in the etiology of AD, including inflammatory responses, synaptic damage, defects in the cholinergic system, abnormalities in the cell cycle, and mitochondrial structural and functional abnormalities [4–12].

Recent research on glycogen synthase kinase 3 beta (GSK3β) revealed that elevated GSK3β activity is directly linked to increased levels of Aβ production and Aβ deposits, tau hyperphosphorylation, and synaptic damage in AD patients and AD animal models [13–17]. It is possible that elevation of GSK3β activity in AD brains and brain tissues from AD mouse models may occur due to Aβ association with insulin, wnt signaling or NMDA receptors [18]. Based on reported multiple cellular and pathological changes, several therapeutic strategies have been used to test agents and drugs on experimental rodent models, and on AD patients, including: Aβ-immunotherapy [19–21], anti-inflammatory therapy [22–25], antioxidant therapy [26–36], cholinergic therapy [37–44], cell cycle therapy [45–47], hormonal therapy [48–50], and inhibition of GSK3β activity [13–17] (Fig. 1). Although tremendous progress has been made in understanding the AD progression and pathogenesis, and in developing therapeutic strategies, we still not have agents or drugs that can slow or prevent AD progression.

The purpose of this article is to review the latest developments of GSK3β involvement in AD pathogenesis, particularly its association with mitochondria in causing mitochondrial dysfunction and neuronal damage. We also review and discuss GSK3β involvement in phosphorylation of VDAC1 and dissociating VADC1 with hexokinases in AD neurons.

2. Mitochondrial dysfunction and Alzheimer's disease

Mitochondrial dysfunction is a prominent and early cellular change in AD pathogenesis, but the precise mechanism underlying this dysfunction is still not completely understood. Mitochondrial abnormalities and oxidative stress have been extensively described in AD pathogenesis [2,11,12] (Fig. 2). Research on mitochondrial function revealed increased free radical production, lipid peroxidation,

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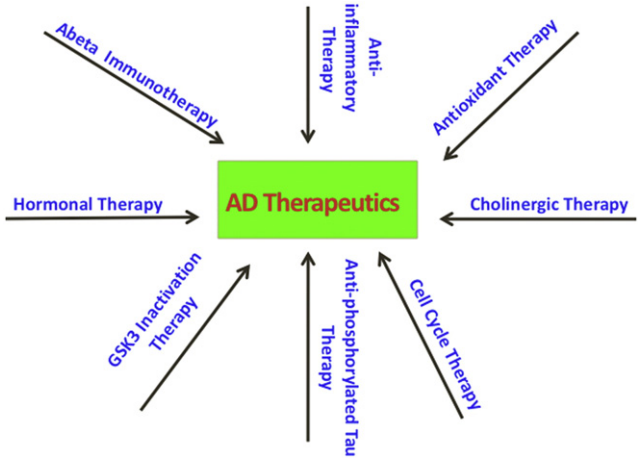

Fig. 1. Therapeutic strategies in Alzheimer's disease. Based on these cellular and pathological changes, multiple therapeutic strategies have been developed, including Aβ-immunotherapy, anti-phosphorylated tau therapy, anti-inflammatory therapy, anti-oxidant therapy, cholinergic therapy, cell cycle therapy, hormonal therapy, and inhibition of GSK3β activity.

mitochondrial fission-linked GTPase activity, oxidative DNA, protein damage, and reduced ATP production and cytochrome oxidase activity in postmortem AD-affected brain tissues [51–56]. Further, using biochemical, molecular, gene expression, and electron microscopy studies, and postmortem AD brains and brains from AβPP mice, several studies found that Aβ is associated with mitochondrial dysfunction and neuronal damage [51,57–67]. Recent research also revealed that phosphorylated tau is critically involved in defective axonal transport of mitochondria, synaptic deprivation, oxidative stress, and abnormal mitochondrial dynamics in AD pathogenesis [68,69]. A recent study reported that, in postmortem AD brains and brain tissues from AβPP mice, Aβ (monomers and oligomers) and phosphorylated tau interacted with the mitochondrial outer membrane protein VDAC1 [62], suggesting that Aβ and/or phosphorylated tau may block the transport of organelles between mitochondria and

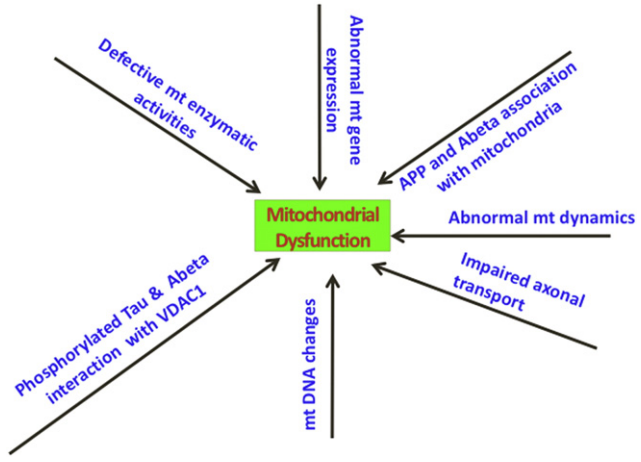

Fig. 2. Mitochondrial abnormalities in Alzheimer's disease pathogenesis. Multiple mitochondrial abnormalities have been identified in Alzheimer's disease pathogenesis, including abnormal mitochondrial gene expression, defective mitochondrial enzymatic activities, accumulation of somatic mitochondrial DNA changes, abnormal mitochondrial dynamics, impaired mitochondrial axonal transport, amyloid beta and amyloid precursor protein association with mitochondria, and amyloid beta and phosphorylated tau interaction with mitochondrial outer membrane protein, VDAC1. Research on mitochondrial function revealed increased free radical production, lipid peroxidation, mitochondrial fission-linked GTPase activity, oxidative DNA, and protein damage, and reduced ATP production and cytochrome oxidase activity in postmortem Alzheimer's disease-affected brain tissues and tissues from Alzheimer's disease mouse models and peripheral tissues and cell models of Alzheimer's disease.

the cytoplasm possibly causing defects in oxidative phosphorylation and mitochondrial ATP synthesis. It is unclear how Aβ and phosphorylated tau each interact with VDAC1, and how these interactions may lead to oxidative phosphorylation defects and the reduction of ATP synthesis in neurons affected by AD.

3. VDAC1 and Alzheimer's disease

VDAC, which is ubiquitously located in the mitochondrial outer membrane, is generally thought to be the primary means by which metabolites diffuse in and out of mitochondria [70–72]. Three VDAC isoforms (VDAC1, VDAC2, and VDAC3) have been found in mammalian mitochondria. Of these isoforms, VDAC1 is the most widely expressed, followed by VDAC2, and then VDAC3 [73,74]. The relevance of VDAC2 and VDAC3 is minimal for neurodegenerative diseases such as AD, PD and HD because of their low expressions in neurons.

VDAC proteins perform several important functions in the cell, including maintaining synaptic plasticity and mitochondrial permeability transition (MPT) pore; and regulating the shape and structure of mitochondria, hexokinase interactions with mitochondria, and apoptosis signaling [75,76]. The change in mitochondrial permeability that is characteristic of apoptosis is mediated by the Bcl-2 family of proteins, which binds to VDAC and alters channel kinetics and conductance [75]. Recent research also revealed that VDAC is inhibited by the cytoskeletal protein tubulin, resulting in impairments in channel conductance [77]. In addition, several recent studies revealed that VDAC proteins and their binding partners are modified post-translationally due to VDAC phosphorylation and are involved in VDAC dysfunction [78,79]. However, the causal factors of VDA1phosphorylation in AD pathogenesis are not completely understood.

Di Pinto and colleagues [80] studied the role of alpha-helix of VDAC1 in pore activity. They synthesized the human VDAC1 N-terminal peptide Ac-AVPPTYADLGKSARDVFTK-NH2 (Prn2-20) and determined its structure by circular dichroism (CD) and nuclear magnetic resonance spectroscopy. CD studies showed that the Prn2-20 peptide exists in an aqueous solvent as an unstructured peptide without stable secondary structure. No ordered structure was observed in dodecyl beta-maltoside. Differential scanning calorimetric measurements were carried out in order to examine the membrane affinity of VDAC. Upon the interaction with the negatively charged 1,2 dipalmitoyl-sn-glycero-3-phosphoserine membrane, Prn2-20 exhibited distinctive behavior, suggesting that electrostatics may play an important role. Interaction between the peptide and artificial bilayers indicates that Prn2-20 lies on the membrane surface. Recombinant HVDAC1 deletion mutants, devoid of N-terminal amino acid 7 or 19, were used to transfect eukaryotic cells. In studies of N-terminal VDAC structure, in which cells were transfected with human VDAC1 lacking amino acid 7 or 19, the over-expression of human VDAC1 increased the number of COS cells with depolarized mitochondria, which progressively reduced. The mitochondrial targeting of the deletion mutants was unaffected. This study concluded that the VDAC N-terminal peptide plays a role in the proper function of VDAC1 during apoptotic events.

Geula and colleagues [81] studied the location and translocation of the VDAC1 N-terminal domain, and its role in voltage-gating and as a target for anti-apoptotic proteins. They used site-directed mutagenesis and cysteine residue substitution, together with a thiol-specific cross-linker, to determine whether the VDAC1 N-terminal region exists in a dynamic equilibrium and is located fully within the pore or exposed outside the β-barrel. Using a single cysteine-residue-bearing VDAC1, they found that the N-terminal region lies within the pore. However, the region can be exposed outside the β-barrel where it dimerizes with the N-terminal domain of a second VDAC1 molecule. When the N-terminal region α-helix structure was perturbed, intra-molecular cross-linking was abolished and dimerization was enhanced. As a result of this structural change, the mutant form of VDAC1 also displayed reduced voltage-gating and reduced binding to hexokinase, but not to