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Short Communication

Neurophysiological Changes in Oxidative Injury: Involvement of Calcium Homeostasis and ER Stress

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Submitted: 10 December 2016

Accepted: 31 August 2017

Published: 02 September 2017

ISSN: 2378-9565

Keywords

• Azheimer disease; Unfolded protein response

Abstract

Endoplasmic reticulum (ER), a multifunctional organelle, plays an important role in the maintenance of intracellular calcium homeostasis and regulation of cell death. Cellular stress conditions such as glucose deprivation, depletion of ER calcium stores and exposure to free radicals that interfere with ER function lead to the accumulation and aggregation of proteins. ER stress can be developed by disrupting its homeostasis in neurological diseases and by disturbances in calcium or redox status. Thus, increase in the cytosolic calcium is one of the important aspects in brain diseases which may contribute to oxidative stress injury and cell death. ER stress plays a vital role in neuronal cell death.

Azheimer disease (AD) is a common neurodegenerative disease which is a frustrating clinical problem and is one of the leading cause of death worldwide. In neurodegenerative diseases and in aging, free - radical generation is the common cause of tissue injury and cell death. Imbalance between ROS productions and antioxidant levels result in development of oxidative stress which through a series of events deregulates the cellular functions and leads to premature aging. Excessive increase of Ca^{+2} in mitochondrial matrix, the permeability of mitochondria changed and finally resulted in MPT pore opening followed by release of cytochrome C and other proapoptotic factors into the cytoplasm. The released cytochrome C then activates caspase 3 to initiate cell death. ER Stress leads to the activation of unfolded protein response (UPR) and governs the recovery of homeostasis. Otherwise, UPR fails to restore normal function in chronic ER stress and results in apoptosis of irreversibly damaged cells.

In this communication, the role of unfolded protein response (UPR) in neurodegeneration induced ER stress and its modulation will be described. It also will be illustrated the mechanism of age-associated declines in cellular function and progressive failure of chaperoning system. Thus, the protective role of free and nanoformulated compounds in reducing stress generation during AD especially in aging will also be elucidated.

INTRODUCTION

Endoplasmic reticulum (ER) stress induced cell death plays an important role in neurodegenerative diseases. Alzheimer is a patho physiological ER stressor [1-3]. Several studies have shown that AD causes a severe impairment of ER function, which in turn triggers shut down of protein translation and apoptosis [4,5] suggesting that ER plays an important role in Alzheimer diseases. Endoplasmic reticulum (ER) stress plays a vital role in mediating neuronal cell death. Under various pathological situations, these physiological functions of the ER are perturbed resulting in so called ER stress and can lead to the accumulation of the newly synthesized unfolded proteins in the ER. The molecular mechanisms of ER damage in neurodegenerative diseased neurons are not clear [6]. But a number of in vitro studies have demonstrated that ER function is sensitive to oxidative stress [7-9]. The Endoplasmic reticulum (ER) is branched tubule and flattened sac network which is an extension of nuclear envelop and connect to the golgi complex. The ER is also one of the organelle that produces reactive oxygen species (ROS) robustly in the neurodegenerative disorder in the brain [10,11] as a result of oxidative stress. So, ROS are involved in neuronal cell death as they damage the ER. ER has various functions such as protein folding, post translational modification and maintenance of cellular calcium homeostasis [11,12].

Among the stimuli that promote ER stress are ischemia, inflammation and disorders that impair the ER's ability to properly fold peptides or eliminate unfolded proteins [13]. Neurodegenerative disordered diseases such as AD induces ER stress, which is characterized by the accumulation of proteins in the ER [13], leading to the activation of several pathways to restore normal ER function [14]. If, however, ER function is severely impaired and cellular homeostasis cannot be restored, apoptosis of the neuron is induced. ER stress triggers the activation and expression of a number of proteins, including up-regulation of the transcription factor CHOP (C/EBP-homologous protein also known as C/EBP), growth arrest- and DNA damage inducible gene 153 [GADD153] or DNA-damage inducible transcript 3 [DDIT3]). CHOP belongs to the C/EBP transcription factor family and has been shown to trigger apoptosis [15].

Changes in the Ca^{+2} level in the ER elicit ER stress, a universal cellular response, which through three ER sensors (PERK, IRE1α, and ATF6) blocks translation and up regulates genes that

first mount an anti apoptotic response. Only if the disturbance cannot be overcome and the signal persists, apoptosis is induced [16]. A-beta production inhibition or immunization strategies in the first line failed to cure AD. This suggests that ER stress is one of the cellular pathologies induced by AD. Due to increased oxidative stress, accumulation of unfolded proteins and metabolic disturbances are observed in AD [17]. ER is one cellular organelle that is related to stress mediation by its multifunctionality that ER assists and closely related to monitor quality of ascent proteins [18]. To eliminate the toxic protein components cells activate an adaptive mechanism that consist of a number of intracellular signaling pathway collectively known as the unfolded protein response (UPR) [19,20]. However during prolonged or overwhelming ER stress, UPR fails to restore the normal function of the ER and apoptotic cascade will be activated [21-23] .

ER stress can also be initiated by the accumulation of unfolded proteins in the organelle which causes the release of Ca^{+2}. The mitochondrion as well as ER plays an important role in the regulation of cellular calcium homeostasis [24]. Under prolonged ER stress condition as happens in the different neurodegenerative disordered diseases, a slow but sustained increase in the mitochondrial matrix free Ca^{+2} occur, which can reach a critical threshold to trigger the opening of mitochondrial permeability transition pore (MPTP) and initiate the apoptotic cascade [25]. The ER can play an important role in regulating apoptosis by adjusting the load of Ca^{+2} upon the mitochondrion. So, the reduction in Ca^{+2} in the mitochondria which can be released from ER decrease the probability of apoptosis [26-28]. The over expression of the anti apoptotic protein BCL2 can influence the distribution of Ca^{+2} within the ER/mitochondrial complex. Other anti apoptotic protein, AKT also results in reduced ER Ca^{+2} release, and diminished cellular sensitivity to Ca^{+2} mediated apoptotic stimuli [26,29] Anti apoptotic proteins BCL2 and AKT affect calcium homeostasis

By down regulating translation and up regulating transcription of ER resident enzymes and chaperons, UPR acts primarily to protect against ER stress. However the sustained activation of UPR effectors can lead to an apoptotic phenotype via CHOP transcription and translation and by caspase12 activation. It is this "double edged sword" feature of the UPR that has made it as an attractive model as a contributor to cell death. If indeed AD causes ER stress and activates the UPR, the resultant molecular cascades could contribute to either cell survival or death.

Alzheimer disease, a progressive neurodegenerative disorder, leads to dementia by involving a gradual declination of many cognitive processes. Amyloid β peptides and neurofibrillary tangles are accumulated at the onset of AD. ER can recognize disturbances in cellular homeostasis. So, ER stress is an indicator of AD [30] and it plays an important role to reduce AD in the brain. Thus reducing ER stress may provide a process to reduce β peptide accumulation. In this context, it is worth mentioning that many native plant products were found to demonstrate the effectiveness to fight numerous diseases including AD. Based on range, flexibility, ease of access, relatively low cost, low levels of technological input, relative low side effects of traditional medicine (WHO 2002), there is a critical need to mainstream traditional medicine into public health care to achieve the objectives of improved access to healthcare facilities.

So, it is therefore proposed to look into effective therapeutic agents from Indian plants to promote human health by inhibiting different neurodegenerative diseases specially AD. This communication tells us to reduce AD by inhibiting ER stress by using native plant products. Due to limitations posed by the restrictive BBB, it is very difficult to administer required drugs at right concentrations in the diseased cells. Thus, new therapeutics and novel delivery approaches with the capacity to successfully cross the BBB is critically needed. Nanotechnologies hold great promise in AD treatment as the nanoencapsulated drugs can easily cross the BBB, protect therapeutic agents and even allow its sustained release. It has been observed from previous studies [31] that nanovesiculated drug delivery mode was the most effective to combat neurodegenerative disorders in comparison to other vesicular mode. These findings would possibly lead to provide new insights into the molecular pathways of disease and pharmacological manipulation for blocking the disease.

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Cite this article

Sarkar S, Mandal A (2017) Neurophysiological Changes in Oxidative Injury: Involvement of Calcium Homeostasis and ER Stress. JSM Alzheimer's Dis Related Dementia 4(1): 1033.