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RESEARCH ARTICLE

Activation of endoplasmic reticulum stress in rat brain following low-intensity microwave exposure

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Abstract

The present study was designed to explore the effects of low-intensity microwave radiation on endoplasmic reticulum stress and unfolded protein response. Experiments were performed on male Wistar rats exposed to microwave radiation for 30 days at 900 MHz, 1800 MHz, and 2450 MHz frequencies on four groups of animal: sham-exposed group, 900 MHz exposed (SAR 5.84×10^{-4} W/kg), 1800 MHz exposed (SAR 5.94×10^{-4} W/kg), and 2450 MHz exposed (SAR 6.7×10^{-4} W/kg) groups. Expressions of mRNA were estimated at the end of exposure in rat brain by real-time quantitative PCR. Microwave exposure at 900, 1800, and 2450 MHz with respective SAR values as mentioned above significantly (< 0.05) altered mRNA expression of transcription factors ATF4, CHOP, and XBP1 in accordance with increasing microwave frequency. The result of the present study reveals that low-intensity microwave exposure at frequencies 900, 1800, and 2450 MHz induces endoplasmic reticulum stress and unfolded protein response.

Keywords Brain · Microwave · Endoplasmic reticulum stress · Gene expression · Unfolded protein response

Introduction

Today, round the clock 24 × 7, everyone is under constant exposure to microwave radiation due to tremendous increase in the usage of mobile phones. Microwave interacts with biomolecules of living cells like nucleic acids and proteins and thereby damages the biomolecules through generations of reactive oxygen species (ROS) (Megha et al. 2012; Deshmukh et al. 2015). Mobile phones are in close proximity to the brain; therefore, the effect is of serious concern. Polyunsaturated fatty acid content and metabolic rate of the brain are significantly higher as compared to other organs of the body, which makes it highly vulnerable to ROS and oxidative damage (Hermann and Hossmann 1997), since higher unsaturated fatty acid content of the brain makes it prone to peroxidation by generated ROS (Ferrante et al. 2017) and peroxidated lipid is well associated with the neurodegenerative process (Praticò 2002). Low-intensity microwave radiation is an oxidative agent for living systems and as a potential oxidative stress inducer via ROS generation, it might be a potential mechanism of generating ER stress and associated bimolecular alterations.

Endoplasmic reticulum is an important cell organelle actively involved in synthesis and folding as well as processing of secretory and membrane proteins. ER stress arises due to imbalance between protein synthesis and proper folding of protein. ER stress leads to accumulation of unfolded proteins in ER lumen and induces a stress response known as unfolded protein response (UPR) and supports cell survival (Ron and Walter 2007). Transcription factors like Activating transcription factor 4 (ATF4), C/EBP homologous protein (CHOP), and X-box binding protein (XBP1) are well-defined transcription factors which actively participate in ER stress and unfolded protein response to overcome ER stress (Oslowski and Urano 2011). ATF4 is a major regulatory gene, which has a crucial role in stress adaptation by controlling the transcription of genes. CHOP is one of the target genes of ATF4 which regulates the stress-induced gene transcription and amplifies the signals generated by stress. CHOP is also involved in growth arrest of cells. The active form of XBP1 gene is

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truncated mRNA, an important signal transducer in ER stress response. Unsliced XBP1 is constitutively expressed inside cells which performs as a negative feedback regulator of spliced XBP1 (Hetz et al. 2011; Gardner and Walter 2011).

Today's lifestyle and various environmental stresses directly or indirectly induce ER stress and provoke UPR pathway signaling for cell survival by modulation in cell functions (Zhang and Kaufman 2008). In this paper, we discussed ER stress level by assessing the gene expressions of ATF4, CHOP, and spliced XBP1 mRNA level following microwave exposure in Wistar rats. The present study shows the evidence of ER stress generation in rat brain, due to low-intensity microwave exposure with gene expression of candidate transcription factor which is actively involved in the ER stress response regulation.

Material and methods

Microwave generation and exposure conditions

The gigahertz transverse electromagnetic (GTEM) cell was used in the study for exposing animals to microwave radiation. The schematic diagram of microwave exposure system and assembly of associated components for generation of microwave signal inside the TEM cell has been shown in Fig. 1. The GTEM cell was designed with the help of Centre for Applied Research in Electronics (CARE), Indian Institute of Technology, New Delhi, India (Fig. 2). The microwave exposure system was calibrated for various electromagnetic characteristics and uniformity of electric field (E-field). The uniformity of electric field was experimentally validated before exposure by means of an E-field probe (Rohde & Schwarz NRV-Z32, Germany) inserted into the microwave chamber through a slit wall. The GTEM cell was operated in a temperature-controlled room under constant lighting conditions.

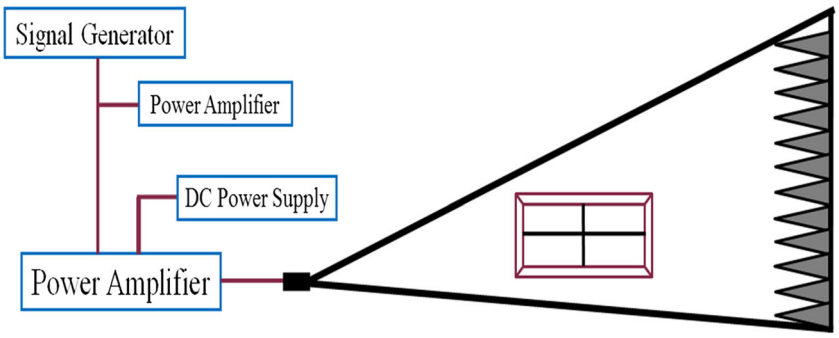
Specific absorption rate measurement

Specific absorption rate (SAR) distribution was calculated by the power balance method as described by Ardoino et al. (2005):

Animal exposure and relative gene expression

Male Wistar rats (weighing 100–150 g) were obtained from the central animal house facility of the institute and placed in individual raised, galvanized wired cages. They were acclimatized to laboratory conditions for 5 days and were kept under standard conditions (temperature 22 ± 2 °C, constant humidity 40–50%) with an alternating 12-h light and dark cycle. Rats were provided with a nutritionally adequate standard diet obtained from Nutri-lab (Bangalore, India) and water ab libitum. The 24 rats were equally divided into four groups: group I (sham exposed), animals kept under the same conditions as that of other groups except microwave exposure; group II, animals exposed to microwave radiation at 900 MHz, SAR 5.84×10^{-4} W/kg; group III, animals exposed to 1800 MHz, SAR 5.94×10^{-4} W/kg; and group IV, animals exposed to 2450 MHz, SAR 6.7×10^{-4} W/kg. At a time, six rats were given whole-body microwave exposure in the GTEM cell (Amitec Electronics Ltd., India) 100 cm away from the source of the microwave signal, and restrained in closed boxes at frequencies 900, 1800, and 2450 MHz (power level 0.00 dBm) for 2 h/day during light period for 6 days/week at the same time for a duration of 30 days. The protocol and study method were approved by the Institutional Animal Ethical Committee, University College of Medical Sciences, Delhi (UCMS/IAEC/CAH/2016/093) and care of the animals was undertaken as per guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals, India.

Immediately after exposure to microwave, animals were decapitated and hippocampi were isolated from ice-cold



Schematic representation of microwave exposure set up

Fig. 1 Schematic flow diagram of the microwave exposure system and assembly of associated components for generation of microwave signal inside the TEM cell



Fig. 2 Laboratory setup of microwave exposure system with signal generator, power meter, and amplifier

PBS buffer-washed brain of individual animals (six rats/group). RNA was isolated from hippocampus tissue using TRIzol reagent (Life Technologies, USA) according to the manufacturer's protocol. A total of 1 μg of RNA was converted into cDNA with oligoDT and random hexamer using Verso cDNA synthesis kit (Thermo Scientific, USA) as per manufacturer's instructions.

Quantitative RT PCR analysis

Quantitative RT PCR (qRT PCR) was performed in a 20 μl volume containing 10 μl of SSO Fast Eva green super mix (Bio-Rad, USA) as per manufacturer's protocol. qRT PCR was carried out on a CFX Connect™ Real-Time system (Bio-Rad, USA). Each sample was run in triplicates. The relative gene expression levels of selected genes in microwave-exposed and sham-exposed groups were determined by comparative ΔΔCt method (Livak and Schmittgen 2001) (Table 1).

Statistical analysis

Values were expressed as mean standard deviation (SD). Significance of differences among groups was determined by one-way analysis of variance (ANOVA) followed by Turkey's post hoc test and Pearson's correlations. Statistical significance was accepted at $p < 0.05$.

Results

The result of gene expression analysis showed that low-intensity microwave exposure induced changes in mRNA levels of transcription factors viz. ATF4, CHOP, and truncated XBP1 involved in the induction of ER stress, and also these transcription factors are markers of ER stress. All the data were normalized to GAPDH housekeeping gene, and similar results were obtained when normalization was done with another housekeeping gene, i.e., β-actin. Analysis of ATF4 and CHOP mRNA expressions revealed that low-intensity microwave exposure upregulates the expression of both transcription factors which is involved in ER stress/UPR significantly ($p < 0.05$) in hippocampus of microwave-exposed animals when compared with sham-exposed animals. However, XBP1 spliced mRNA expression was downregulated significantly in all microwave-exposed animals.

Quantitative real-time PCR results revealed the significant induction in expression level of ATF4 mRNA in hippocampus of the microwave-exposed groups of animals (1.6-fold in 900-MHz–exposed animals, 3.3-fold in 1800-MHz–exposed group of animals, and 3.9-fold in 2450-MHz–exposed animal group) in comparison with the sham-exposed animal group ($p < 0.05$) (Fig. 3). When the 900-MHz–exposed group was compared with 1800-MHz– and 2450-MHz–exposed groups, the difference was significant ($p < 0.05$), whereas when the 1800-MHz– and 2450-MHz–exposed groups were compared to each other, the difference was found statistically insignificant.

The expression level of CHOP mRNA was increased significantly in hippocampus of microwave-exposed rats (1.3-fold in 900-MHz–exposed group of animals, 3.5-fold in 1800-MHz–exposed group of animals, and 3.8-fold in 2450-MHz–exposed animal group) in comparison with the sham-exposed animals ($p < 0.05$) (Fig. 4). When the 900-MHz–exposed group was compared with the 1800-MHz– and 2450-MHz–exposed groups, the difference was significant ($p < 0.05$). However, the 1800-MHz– and 2450-MHz–exposed groups did not show a significant difference between each other.

Table 1 Primer sequences of active transcription factor of ER stress/UPR genes used in quantitative real-time PCR assay

Genes	Primer sequence (5′–3′)	Size (bp)	Annealing temp (°C)
GAPDH (Yang et al. 2012)	**F**-TGCCCCCATGTTTGTGATG **R**-TGGTGGTGCAGGATGCATT	83	55
CHOP	**F**-GAGTGTTCCAGAAGGAAGTGC **R**-TGGACACTGTCTCAAAGGCG	114	59
ATF4 (Oslowski and Urano 2011)	**F**-AATGGATGACCTGGAAACCA **R**-TCTTGGACTAGAGGGGCAAA	84	52
XBP1	**F**-AGTTAAGGACACGCTTGGGG **R**-CACGTAGTCTGAGTGCTGCG	123	54

F forward, *R* reverse

The truncated mRNA expression level of XBP1 was decreased significantly (2.8-fold in 900-MHz–exposed group of animals, 3.6-fold in 1800-MHz–exposed group of animals, and 4.4-fold in 2450-MHz–exposed animal group) in comparison with the sham-exposed animal group ($p < 0.05$) (Fig. 5). When the 900-MHz–exposed group was compared with the 1800-MHz– and 2450-MHz–exposed groups, the difference was significant ($p < 0.05$) for both of them, but the difference was insignificant when the 1800-MHz– and 2450-MHz–exposed groups were compared with each other.

Pearson's correlation analysis revealed that the expression of ATF4 was strongly positively correlated with the expression of CHOP ($r = 0.9$) but negatively correlated with the expression of XBP1 ($r = 0.7$) spliced mRNA; CHOP mRNA was also positively correlated with the expression of ATF4 ($r = 0.9$) mRNA but negatively correlated with XBP1 ($R = 0.6$) spliced mRNA expression.

Discussion

Extensive use of mobile phone communications in day to day life raises a serious public concern regarding the biological ill effects of microwave radiation on the nervous system and human health. Neurodegeneration, impairment in learning & memory, anxiety and stress have been reported with microwave exposure by Deshmukh et al. (2016). The present study was designed to investigate the effect of low-intensity microwave radiation on induction of ER stress in rat brain.

Hippocampus is the main site which is actively involved in cognitive function, behavior, and spatial learning as well as working memory (Rubin et al. 2014). The present study provides two important findings related to low-intensity microwave radiation-induced alterations in gene expression of involved transcription factor which is responsible for ER stress and UPR. Earlier, we have reported oxidative stress (Megha et al. 2012), neurogenotoxicity (Deshmukh et al. 2015), impairment in cognitive functions, heat shock protein stress (Deshmukh et al. 2012), and alterations in different neurotransmitters like dopamine, epinephrine, norepinephrine, and serotonin (Megha et al. 2015) with exposure to microwave radiation of 900, 1800, and 2450 MHz microwave frequencies. However, any correlation of microwave exposure and induction of ER stress/UPR in neurons is lacking in the available literature. Microwave radiation–induced ER stress could be a probable mechanism of cognitive impairment, neuron degeneration, and anxiety. Studies have also reported that long-term microwave frequency exposure in human beings leads to headache, depression, fatigue, and hormonal disorder (Yakymenko et al. 2011). No study so far reported ER stress with reference to low-level microwave exposure and with a wide band of frequencies from 900 to 2450 MHz at a very low SAR.

Neurons are very vulnerable to damage and neurodegeneration occurs as a result of accumulation of damage and lack of repair. Damage repair imbalance leads to pathophysiological conditions. The process of neurogenesis is completed even before birth and most of the regions of the brain form during the gestation period inside the womb, and for the rest of the life, neurons stay in the post-mitotic phase (Guidi et al. 2015). Because of this unique developmental program of neurons, the adult brain has no mechanisms other than autophagy or apoptosis to replace or remove aged and malfunctioning nerve cells due to accumulation of misfolded/unfolded proteins. In the absence of a replacement mechanism inside the adult brain, there is a gradual loss of neurons, thereby affecting mental health of individuals. In this way, microwave can influence release of neurotransmitter, neuronal functions, regulation of synaptic plasticity, and neuronal survival, and hence learning and memory (Esposito and Postle 2015). Salford et al. (2003) reported inhibition of differentiation of neural stem cells into neurons as well as cell death due to EMF exposure during embryonic development (Guidi et al. 2015).

The first important finding from the present study demonstrated that low-intensity microwave radiation exposure at 900, 1800, and 2450 MHz for 30 days induced significant induction in levels of mRNA of gene ATF4 and CHOP in hippocampus of experimental animals, substantiating that

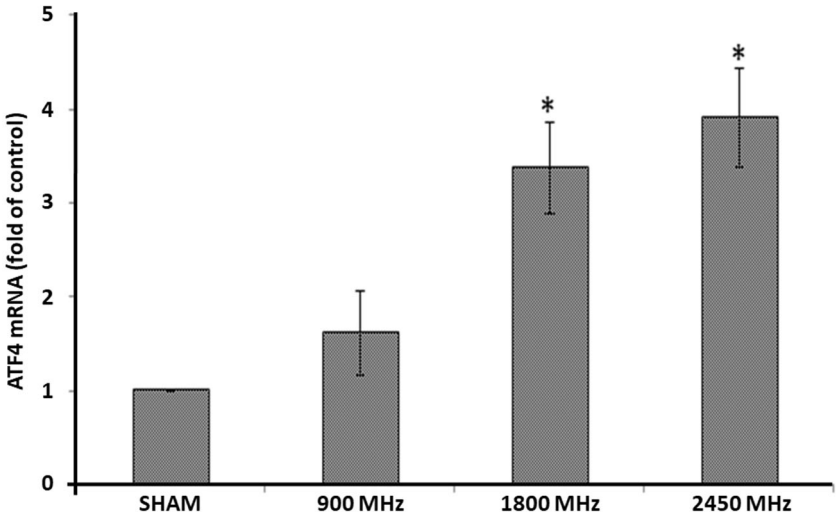


Fig. 3 Fold change of ATF4 gene expression in hippocampus following low-intensity microwave exposure. Significant differences between microwave-exposed and sham-exposed groups are indicated by *asterisk* ($p = 0.001$). Values are expressed as mean ± SD

low-intensity microwave radiation is able to modify synthesis of the transcription factors, thereby leading to their increased levels in brain. Since these transcription factors ATF4 and CHOP play an important role in ER stress/UPR, the induction in the levels of ATF4 and CHOP can be strongly associated with ER stress and UPR.

Upregulated CHOP targeted calcium channel and induced release of Ca^{2+} from ER lumen via regulation of ERO1α expression to mitochondria. Lowering of Ca^{2+} impairs protein folding inside ER lumen, thereby initiating UPR and developing ER stress (Botta et al. 2013). Disulfide bond formation plays a very important part in protein folding. Inside ER lumen, disulfide bond formation is facilitated due to the presence of oxidizing environment factors like ATP and Ca^{2+} for proper protein folding, and ER is highly sensitive to stress in terms of cellular energy, redox environment, and concentration of Ca^{2+} (Li et al. 2009; Hetz 2012).

UPR overcomes ER stress either by decreasing protein translation rate or by increasing degradation of faulty proteins. UPR enhances protein folding capacity, to alleviate the ER stress. Signaling of UPR is initiated by three different ER membrane-bound transducers: IRE1 (inositol-requiring enzyme 1), ATF6 (Activating transcription factor 6), and PERK (protein kinase-like ER kinase). UPR attempts to help stressed cells in their survival from ER stress by reprogramming in transcription and translation. However, failure in maintaining the unstressed conditions of UPR initiates apoptosis, that is programmed cell death signaling, and neurodegeneration occurs (Dandekar et al. 2015).

Secondly, we obtained a downregulation of spliced XBP1 mRNA in the microwave-exposed animal groups at all given frequencies of 900, 1800, and 2450 MHz. Diminished level of active XBP1 hampers the chaperonic activity and reduces the protein folding capacity as well as degradation of misfolded protein. XBP1 has a protective role in cell survival by maintaining the proper protein folding via chaperons. A diminished amount of active XBP1 ultimately leads to accumulation of misfolded or unfolded protein inside the ER lumen of the

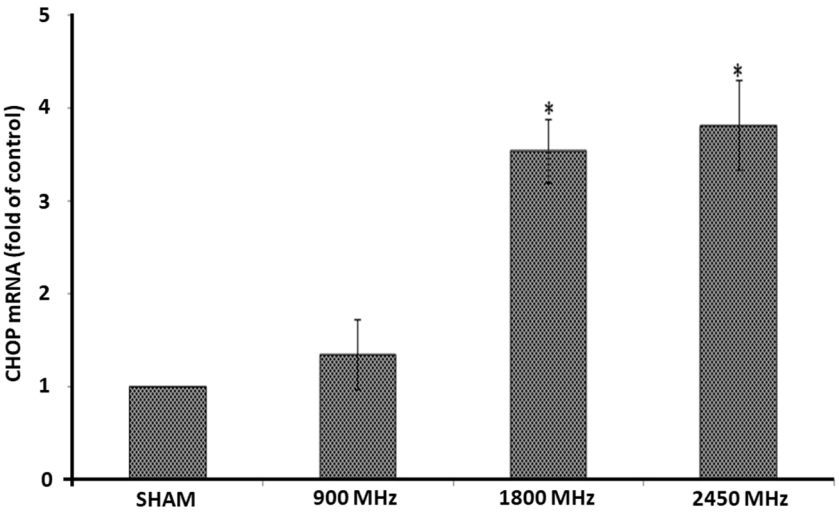


Fig. 4 Fold change of CHOP gene expression in hippocampus following low-intensity microwave exposure. Significant differences between microwave-exposed and sham-exposed groups are indicated by *asterisk* (for 900 MHz, $p = 0.01$; for 1800 and 2450 MHz, $p = 0.002$). Values are expressed as mean ± SD

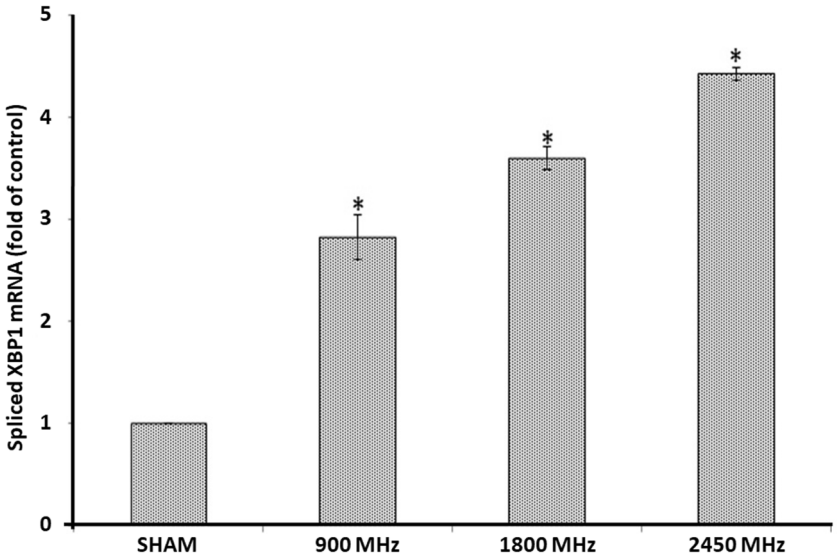


Fig. 5 Fold change of spliced XBP1 gene expression in hippocampus following low-intensity microwave exposure. Significant differences between microwave-exposed and sham-exposed groups are indicated by *asterisk* ($p = 0.004$). Values are expressed as mean ± SD

neuron cell and ER stress develops due to low-intensity microwave exposure. IRE1α is a highly conserved transducer which has a kinase as well as an endoribonuclease property. IRE1α loses RNase activity due to homo-dimerization and auto-phosphorylation under ER stress condition. Activated IRE1α catalyzes splicing of mRNA, which encodes activated XBP1 protein, a potent transcription factor which activates expression of various chaperones as well as enzymes that facilitate folding of proteins, secretion of properly folded proteins, and degradation of misfolded or faulty proteins (Lee et al. 2003). In eukaryotic cells, damaged proteins initiate this signal response, i.e., ER stress/UPR. Cellular homeostasis disturbance is sensed by ER and starts cascades of ER stress pathway (Tsang et al. 2010).

The finding of the present study shows low-intensity microwave 900, 1800, and 2450 MHz significantly upregulate the expression of ATF4 gene. The increased amount of ATF4 signifies increased phosphorylation of eIF2α. PERK phosphorylates eukaryotic translation initiation factor 2 alpha (eIF2α) under ER stress condition. Phosphorylated eIF2α halts protein translation and reduced protein translation alleviates protein folding burden of ER. Phosphorylated eIF2α also mediates translation of activating trans-activator ATF4, which facilitates expression of pro-apoptotic factor CHOP/GADD153, and leads to ER stress-induced apoptosis. Microwave exposure along with ATF4 is also able to induce CHOP gene expression and brings ER stress–induced apoptosis and increases the neuron degeneration. However, ATF4 and CHOP expressions are independent from each other; expression of GADD34 is under the influence of CHOP and ATF4 (Fusakio et al. 2016). ATF4 is also able to induce expression of growth arrest and DNA damage inducible protein GADD34. Whereas GADD34 works on negative feedback regulation in PERK/eIF2a UPR pathway and regulate protein translation (Ma and Hendershot 2003).

Neurons are highly specialized cells and, unlike other cell types, neurons permanently cease their capacity to divide once neuron cells are differentiated. In the adult nervous system, neurons are in a quiescent state (Frade and Ovejero-Benito 2015). Accumulation of misfolded/unfolded protein triggers ER stress in neurons and thereby initiates UPR to overcome this ER stress. However, in the lack of restoring homeostasis inside ER lumen, UPR triggers programmed cell death. Persistent ER stress and gradual loss of neurons are responsible for mental health illness.

In the present study, increasing the expression of ATF4 and CHOP ultimately induces the ER stress and UPR which is supported by the reduction in expression of active form of XBP1 protein. ATF4 and CHOP are integral members of the UPR signaling pathway activated by ER stress (Ron and Harding 2012). As long as cell homeostasis is maintained, the level of spliced mRNA of XBP1 is higher, but as soon as ER undergoes any imbalance between protein synthesis and folding of protein, there is activation of unfolded protein response and ER stress arises inside cells. Disturbed homeostasis induces the transcription of ATF4 and CHOP to relieve the ER stress whereas reduction in the active form of XBP1 reduces the chaperonic activity of cell and thereby further increasing the misfolded or unfolded protein accumulation inside the lumen of ER. A prolonged stress condition further initiates the cascades of apoptosis signaling and thereby neuron degeneration accelerates leading to cognitive impairment (Fig. 6). Conclusively, microwave induces ROS which assisted in protein misfolding/unfolding inside ER lumen and brings reduction in active form of XBP1 protein and increases the expression of other transcription factors ATF4 and CHOP protein. This further leads to cell growth arrest, DNA damage, and finally cell apoptosis to remove the stress condition arising from microwave-induced ROS. We noted MW affects ER stress at the mRNA level; however, we have not

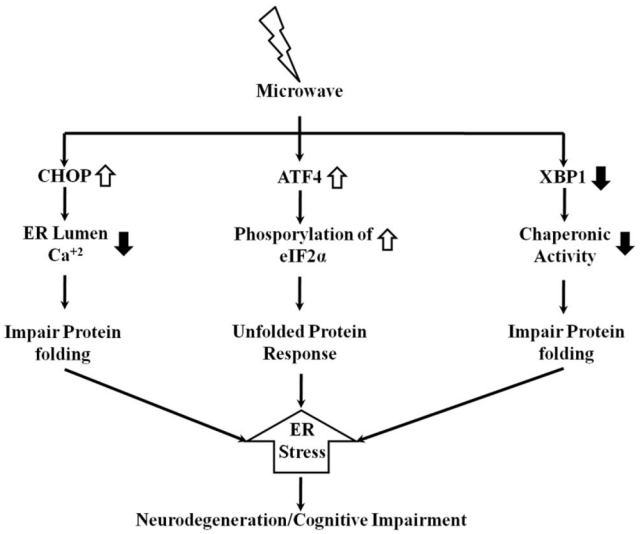


Fig. 6 Schematic representation of microwave association with ER stress marker gene expression in neurodegeneration/cognitive impairment. Microwave exposure up regulates CHOP and ATF4 gene whereas downregulates spliced XBP1 gene. Thereby impairment in protein folding process and generation of ER-Stress

studied these factors with different doses and duration, hence we are planning to do it in the next phase of study, in order to get the concrete idea of frequency and duration in ER stress and their signaling process.

Here, we are reporting for the first time microwave exposure–induced ER stress effect. The present study provides strong evidence for extreme sensitivity of brain ER stress to low-intensity microwave radiation in the range of 900 to 2450 MHz. Thus, it is suggested that alterations caused in these transcription factors of ER stress at mRNA levels following low-intensity microwave exposure might be the possible cause for cognitive impairment and memory dysfunction.

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Compliance with ethical standards

The protocol and study method were approved by the Institutional Animal Ethical Committee, University College of Medical Sciences, Delhi (UCMS/IAEC/CAH/2016/093) and care of the animals was undertaken as per guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals, India.

Conflict of interest The authors declare that they have no conflict of interest.

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