BRIEF REPORT on the ALZHEIMER'S DISEASE and CELL PHONE RADIATION EXPOSURES

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Note: This is not a comprehensive review of the published studies.

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One of the debated health effects of the chronic exposures to cell phone radiation (RF-EMF) is possible effect on the Alzheimer's disease (AD).

To date only a limited number of studies were published in this area of research and the evidence of any link between exposures and the AD is weak and contradictory.

Some of the published studies suggest that cell phone radiation might cause/enhance development of the AD, whereas other studies suggest that exposures to cell phone radiation have no effect whatsoever on the development of the AD. There are also studies suggesting that the cell phone radiation exposures might prevent the development and progression of the AD or even reverse the severity of the AD symptoms.

Here is a list of to date published experimental studies on AD and EMF (exposures over 10 MHz, including wireless communication devices):

1. 2016. Kim JY, Kim HJ, Kim N, Kwon JH, Park MJ. Effects of radiofrequency field exposure on glutamate-induced oxidative stress in mouse hippocampal HT22 cells. Int J Radiat Biol 93 (2): 249-256
2. 2016. He GL, Luo Z, Shen TT, Li P, Yang J, Luo X, Chen CH, Gao P, Yang XS. Inhibition of STAT3- and MAPK-dependent PGE2 synthesis ameliorates phagocytosis of fibrillar beta-amyloid peptide (1-42) via EP2 receptor in EMF-stimulated N9 microglial cells. J Neuroinflammation 13 (1): 296
3. 2016. Son Y, Jeong YJ, Kwon JH, Choi HD, Pack JK, Kim N, Lee YS, Lee HJ. 1950 MHz radiofrequency electromagnetic fields do not aggravate memory deficits in 5xFAD mice. Bioelectromagnetics 37 (6): 391-399
4. 2016. Lee JS, Kim JY, Kim HJ, Kim JC, Lee JaS, Kim N, Park MJ. Effects of combined radiofrequency field exposure on amyloid-beta-induced cytotoxicity in HT22 mouse hippocampal neurones. J Radiat Res 57(6):620-626
5. 2015. Zhao YL, Li YX, Ma HB, Li D, Li HL, Jiang R, Kan GH, Yang ZZ, Huang ZX. The Screening of Genes Sensitive to Long-Term, Low-Level Microwave Exposure and Bioinformatic Analysis of Potential Correlations to Learning and Memory. Biomed Environ Sci 28 (8): 558-570
6. 2015. Gramowski-Voss A, Schwertle HJ, Pielka AM, Schultz L, Steder A, Jügelt K, Axmann J, Pries W. Enhancement of cortical network activity in vitro and promotion of GABAergic neurogenesis by stimulation with an electromagnetic field with a 150 MHz carrier wave pulsed with an alternating 10 and 16 Hz modulation. Front Neurol 6: 158-1-158-12
7. 2015. Jeong YJ, Kang GY, Kwon JH, Choi HD, Pack JK, Kim N, Lee YS, Lee HJ. 1950 MHz Electromagnetic Fields Ameliorate Abeta Pathology in Alzheimer's Disease Mice. Curr Alzheimer Res 12 (5): 481-492
8. 2015. Fasseas MK, Fragopoulou AF, Manta AK, Skouroliakou A, Vekrellis K, Margaritis LH, Syntichaki P. Response of Caenorhabditis elegans to wireless devices radiation exposure. Int J Radiat Biol 91 (3): 286-293
9. 2014. Maaroufi K, Had-Aissouni L, Melon C, Sakly M, Abdelmelek H, Poucet B, Save E. Spatial learning, monoamines and oxidative stress in rats exposed to 900 MHz electromagnetic field in combination with iron overload. Behav Brain Res 258: 80-89
10. 2013. Banaceur S, Banasr S, Sakly M, Abdelmelek H. Whole body exposure to 2.4 GHz WIFI signals: Effects on cognitive impairment in adult triple transgenic mouse models of Alzheimer's disease (3xTg-AD). Behav Brain Res 240: 197-201
11. 2013. Jiang DP, Li J, Zhang J, Xu SL, Kuang F, Lang HY, Wang YF, An GZ, Li JH, Guo GZ. Electromagnetic pulse exposure induces overexpression of beta amyloid protein in rats. Arch Med Res 44 (3): 178-184
12. 2012. Arendash GW, Mori T, Dorsey M, Gonzalez R, Tajiri N, Borlongan C. Electromagnetic Treatment to Old Alzheimer's Mice Reverses beta-Amyloid Deposition, Modifies Cerebral Blood Flow, and Provides Selected Cognitive Benefit. PLoS One 7 (4): e35751

13. 2011. Dragicevic N, Bradshaw PC, Mamcarz M, Lin X, Wang L, Cao C, Arendash GW. Long-term electromagnetic field treatment enhances brain mitochondrial function of both Alzheimer's transgenic mice and normal mice: a mechanism for electromagnetic field-induced cognitive benefit? Neuroscience 185: 135-149
14. 2010. Arendash GW, Sanchez-Ramos J, Mori T, Mamcarz M, Lin X, Runfeldt M, Wang L, Zhang G, Sava V, Tan J, Cao C. Electromagnetic field treatment protects against and reverses cognitive impairment in Alzheimer's disease mice. J Alzheimers Dis 19 (1): 191-210
15. 2009. Del Vecchio G, Giuliani A, Fernandez M, Mesirca P, Bersani F, Pinto R, Ardoino L, Lovisolo GA, Giardino L, Calza L. Effect of radiofrequency electromagnetic field exposure on in vitro models of neurodegenerative disease. Bioelectromagnetics 30 (7): 564-572
16. 2008. Perez FP, Zhou X, Morisaki J, Jurivich D. Electromagnetic field therapy delays cellular senescence and death by enhancement of the heat shock response. Exp Gerontol 43 (4): 307-316
17. 2005. Chang IF, Hsiao HY. Induction of RhoGAP and pathological changes characteristic of Alzheimer's disease by UAHFEMF discharge in rat brain. Curr Alzheimer Res 2 (5): 559-569
18. 1993. Omura Y, Losco M. Electro-magnetic fields in the home environment (color TV, computer monitor, microwave oven, cellular phone, etc) as potential contributing factors for the induction of oncogene c-fos Ab1, oncogen c-fos Ab2, integrin alpha5 beta1 and development of cancer, as well as effects of microwave on amino acid composition of food and living human brain. Acupunct Electrother Res 18 (1): 33-73

Of these studies only several were executed in vivo, using different animal models, different radiation exposures and varying exposure protocols. Additional limitation, in all of the animal studies, is a relatively small number of animals per experimental group. This all causes that the available scientific database to evaluate the possibility of the existence of a link between Alzheimer's disease pathology and cell phone radiation exposures is very limited and drawing any human health-related hypotheses is very problematic.

Table below lists to date (February 2017) executed in vivo experimental studies on AD and exposures to cell phone radiation (RF-EMF).

Experimental model	Exposure	Examined property	Effect	Reference
5xFAD transgenic mice – AD model	W-CDMA; 1950 MHz SAR – 5 W/kg mean	Memory; Metabolism beta-amyloid protein	**No effect**	Son Y, et al. Bioelectromagnetics 37, 2016, 391-399
C. elegans strain CL4176 – AD model	DECT, WiFi, GSM; 1,790–2,480 MHz	Paralysis of worm	**No effect**	Fasseas MK, et al. Int J Radiat Biol 91, 2015, 286-293
5xFAD transgenic mice - AD model	1950 MHz; SAR 5W/kg	Reduction of beta-amyloid plaques	**Yes effect**; reduction of AD pathology	Jeong YJ, et al. Curr Alzh. Res 12, 2015, 481-492
rats	900 MHz; SAR 0.05 – 0.18 W/kg; whole body	Learning & memory; oxidative stress; brain metabolism	**Yes effect**; brain metabolism; **No effect**; learning, memory, oxidative stress	Maaroufi K, et al. Behav Brain Res 258, 2014, 80-89
3xTG-AD transgenic mice; AD model	2.4 GHz, WLAN 1.6 W/kg	Cognitive function and anxiety	**Yes effect;** improved cognition, reduced anxiousness	Banaceur S, et al. Behav Brain Res 2013; 240: 197-201
AβPPsw+PS1 transgenic mice; AD model	GSM; 918 MHz, SAR - 0.25-1.05W/kg	Reduction of beta-amyloid plaques	**Yes effect**	Arendash GW, et al. PLoS One 7, 2012, e35751
AβPPsw+PS1 transgenic mice; AD model	GSM; 918 MHz, SAR - 0.25-1.05 W/kg	Mitochondrial function	**Yes effect**; enhances brain mitochondrial function	Dragicevic N, et al. Neuroscience 185, 2011, 135-149
AβPPsw+PS1 transgenic mice; AD model	GSM; 918 MHz, SAR - 0.25-1.05 W/kg	Brain beta-amyloid plaques	**Yes effect**; reduction of beta-amyloid plaques	Arendash GW, et al. J Alzheimers Dis 19, 2010, 191-210

Several of the most recent studies came from the South Korean research group led by H.J. Lee. The other set of important studies was published by the team led by G. Arendash and by S. Banaceur and co-workers.

Studies published by the S. Korean scientists seem to provide a contradictory evidence on AD and RF-EMF. The studies published in 2016 indicate lack of effect of RF-EMF exposure on AD. One of these studies was an in vivo study using transgenic mice (Son Y et al, 2016) and the other was an in vitro study using neurons isolated from the transgenic mice (Lee JS, et al. 2016). However, an earlier study published in 2015 (Jeong YJ et al. 2015) suggest that RF-EMF exposures have beneficial impact on transgenic AD mice. This result, of beneficial impact of cell phone radiation exposure on AD, confirms observations indicating that RF-EMF exposures might be used for the clinical

treatment of AD, as suggested by studies of Arendash et al. and Banaceur et al. (Arendash GW et al. 2010, Dragicevic N et al. 2011, Arendash GW et al. 2012, Banaceur S et al. 2013).

In this 2016 study Korean researches found no effect whatsoever of the RF-EMF radiation on transgenic AD mice when they concluded that: "*These findings indicate that 3-month RF-EMF exposure did not affect Ab-related memory impairment or Ab accumulation in the 5xFAD Alzheimer's disease model"*.

Bioelectromagnetics. 2016 Sep;37(6):391-9. doi: 10.1002/bem.21992. Epub 2016 Jul 19.

1950 MHz radiofrequency electromagnetic fields do not aggravate memory deficits in 5xFAD mice.

Son Y[1], Jeong YJ[1], Kwon JH[2], Choi HD[2], Pack JK[3], Kim N[4], Lee YS[5], Lee HJ[1].

⊕ Author information

Abstract

The increased use of mobile phones has generated public concern about the impact of radiofrequency electromagnetic fields (RF-EMF) on health. In the present study, we investigated whether RF-EMFs induce molecular changes in amyloid precursor protein (APP) processing and amyloid beta (Aβ)-related memory impairment in the 5xFAD mouse, which is a widely used amyloid animal model. The 5xFAD mice at the age of 1.5 months were assigned to two groups (RF-EMF- and sham-exposed groups, eight mice per group). The RF-EMF group was placed in a reverberation chamber and exposed to 1950 MHz electromagnetic fields for 3 months (SAR 5 W/kg, 2 h/day, 5 days/week). The Y-maze, Morris water maze, and novel object recognition memory test were used to evaluate spatial and non-spatial memory following 3-month RF-EMF exposure. Furthermore, Aβ deposition and APP and carboxyl-terminal fragment β (CTFβ) levels were evaluated in the hippocampus and cortex of 5xFAD mice, and plasma levels of Aβ peptides were also investigated. In behavioral tests, mice that were exposed to RF-EMF for 3 months did not exhibit differences in spatial and non-spatial memory compared to the sham-exposed group, and no apparent change was evident in locomotor activity. Consistent with behavioral data, RF-EMF did not alter APP and CTFβ levels or Aβ deposition in the brains of the 5xFAD mice. These findings indicate that 3-month RF-EMF exposure did not affect Aβ-related memory impairment or Aβ accumulation in the 5xFAD Alzheimer's disease model. Bioelectromagnetics. 37:391-399, 2016. © 2016 The Authors Bioelectromagnetics published by Wiley Periodicals, Inc. on behalf of Bioelectromagnetics Society.

In this study the 1.5 months old animals were exposed for 3 months to RF-EMF.

In this 2015 Korean study, observations of G. Arendash were confirmed and the authors concluded that: "*RF-EMF can have a beneficial influence on AD*".

Curr Alzheimer Res. 2015;12(5):481-92.

1950 MHz Electromagnetic Fields Ameliorate Aβ Pathology in Alzheimer's Disease Mice.

Jeong YJ, Kang GY, Kwon JH, Choi HD, Pack JK, Kim N, Lee YS, Lee HJ[1].

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Abstract

The involvement of radiofrequency electromagnetic fields (RF-EMF) in the neurodegenerative disease, especially Alzheimer's disease (AD), has received wide consideration, however, outcomes from several researches have not shown consistency. In this study, we determined whether RF-EMF influenced AD pathology in vivo using Tg-5xFAD mice as a model of AD-like amyloid β (Aβ) pathology. The transgenic (Tg)-5xFAD and wild type (WT) mice were chronically exposed to RF-EMF for 8 months (1950 MHz, SAR 5W/kg, 2 hrs/day, 5 days/week). Notably, chronic RFEMF exposure significantly reduced not only Aβ plaques, APP, and APP carboxyl-terminal fragments (CTFs) in whole brain including hippocampus and entorhinal cortex but also the ratio of Aβ42 and Aβ40 peptide in the hippocampus of Tg-5xFAD mice. We also found that parenchymal expression of β-amyloid precursor protein cleaving enzyme 1(BACE1) and neuroinflammation were inhibited by RF-EMF exposure in Tg-5xFAD. In addition, RF-EMF was shown to rescue memory impairment in Tg-5xFAD. Moreover, gene profiling from microarray data using hippocampus of WT and Tg- 5xFAD following RF-EMF exposure revealed that 5 genes (Tshz2, Gm12695, St3gal1, Isx and Tll1), which are involved in Aβ, are significantly altered inTg-5xFAD mice, exhibiting different responses to RF-EMF in WT or Tg-5xFAD mice; RF-EMF exposure in WT mice showed similar patterns to control Tg-5xFAD mice, however, RF-EMF exposure in Tg- 5xFAD mice showed opposite expression patterns. These findings indicate that chronic RF-EMF exposure directly affects Aβ pathology in AD but not in normal brain. Therefore, RF-EMF has preventive effects against AD-like pathology in advanced AD mice with a high expression of Aβ, which suggests that RF-EMF can have a beneficial influence on AD.

In this study the 1.5 months old animals were exposed to RF-EMF for 8 months, what is much longer than the exposure of the animals in the 2016 study that produced no-effect outcome.

Because in both South Korean studies animals of the same age were exposed to the same radiation using the same exposure protocol. The single exception was that in one study animals were exposed for 3 months and in the other for 8 months. The longer exposure produced an effect whereas the shorter exposure did not. This may suggest that in order to obtain any potentially therapeutic outcome of the RF-EMF exposure in the transgenic AD model mice, longer exposure periods are necessary. Lengthening of the RF-EMF exposure period might also lead to development of side effects, such as potentially higher susceptibility to develop e.g. brain cancer or leakage of the blood-brain barrier.

The most spoken about is a series of studies from the laboratory of Gary Arendash, suggesting that exposures to RF-EMF might have beneficial, even therapeutic, effects on the Alzheimer's disease (AD).

The relative importance of the research by Arendash's group is enhanced by the fact that this group is currently conducting a human trial that will/might provide some much needed evidence to corroborate, or to dismiss, G. Arendash's claims The protocol of the human study can be reviewed on the ClinicalTrials.gov website run by the US National Instituted of Health (https://clinicaltrials.gov/ct2/show/NCT02958930?id=02958930&rank=1).

Few critical assessments of the work by Gary Arendash and co-workers:

1. The set up used to expose the animals in the AD studies was extremely crude. Animals were exposed from the distance. The radiation dose received by each animal is unknown.

   This differs significantly from the exposure set-up in the clinical trial where the exposure device is placed directly on the head of the patient.

   Already at the time of the first publication by Arendash et al., the exposure set-up for the mice was strongly criticized within the bioelectromagnetics community.

   The crudeness of the exposure set-up makes it impossible to determine how much radiation each animal received. This might be problematic for the replication studies because it will be difficult to exactly replicate the exposure conditions when the level of radiation exposure of animals is practically unknown. While it is easy to set cages around the antenna, it is very difficult to determine radiation exposure of each animal.

   However, the crudeness of the exposure set-up doesn't automatically invalidate the obtained results. In 2011, during the discussions at the IARC meeting for the classification of the carcinogenicity of cell phone radiation, Niels Kuster pointed out that if there is a clear difference between unexposed controls and exposed models, the result should be considered as valid, even though the exposure set-up is crude and it might be very difficult to exactly replicate strength of the exposure in subsequent studies.

2. G. Arendash considers that the beneficial effect of RF-EMF exposure on transgenic AD mice model was of a non-thermal nature. Indeed, looking at the very low level of the estimated exposure (1.05 W/kg at the highest) and the distance between the antenna and the animals in cages, it is pretty obvious that the exposure could not cause any thermal effects. Because result of Arendash et al. was confirmed in studies by Banaceur et al. and by Jeong et al. it might be considered as a **replicated proof of the existence of non-thermal effects**. However, ICNIRP and the WHO do not recognize this evidence of non-thermal effect as proven but only as a hypothesis (as stated by Rodney Croft at the Science & Wireless meeting in Melbourne, Australia in 2016).

3. Two potential biological mechanisms were suggested, by G. Arendash, to explain the observed therapeutic effect of RF-EMF exposure on AD in mice:

   - Direct effect of radiation, causing vibration of H-bonds in beta-sheet proteins, weakening the bonds in amyloid-oligomers leading to their disaggregation (the oligomers are toxic to neurons, not the plaques).
   - Indirect effect (radiation affects unknown yet target inside cells that, in turn, causes increased expression of Hsps), where therapeutic effect is elicited through the increased expression of Hsp70 and Hsp90.

   While changes in the expression of Hsps were shown in several other studies and, thus, the hypothesis might be plausible, the impact on RF-EMF on the vibration of H-bonds, causing disintegration of the aggregated beta-amyloid proteins, is highly controversial because of the radiation energy considerations.

4. Safety considerations for the RF-EMF therapy for AD

   There are numerous studies suggesting that RF-EMF exposures might have (possibly or probably) negative impact on human health. Therefore, when planning a long-term treatment of AD patients this aspect needs to be taken into consideration.

G. Arendash, however, in spite of the existing evidence to the contrary, has completely dismissed any possibility of causal link between RF-EMF exposure and ill health. In his opinion, the long-term therapy of AD with RF-EMF will have no side effects in form of e.g. brain cancer or leakage of the blood-brain barrier.

G. Arendash claims that there are no effects of RF-EMF exposure on cognition, immune function, oxidative stress, blood-brain barrier and DNA damage. G. Arendash repeats the misleading claim that cancer cannot be caused by RF-EMF exposures because the energy is too low to break chemical bonds. The "chemical bonds" story, however, appears to contradict the Arendash's own hypothetical mechanism how the AD therapy works - his claim that RF-EMF exposure causes vibration of H-bonds in beta-sheet proteins, weakening the bonds in amyloid-oligomers leading to their disaggregation. Question is why similar mechanism of weakening h-bonds could not be considered for the abundant and functionally essential H-bonds in DNA double-helix? As mentioned above, energy considerations of the RF-EMF exposure make this H-bond-weakening hypothesis not plausible, at least when considering what is known now about the energy needed to affect bonds in molecules.

The safety issue of the AD therapy should be looked at differently. AD is a disease of an old age. Even if the long-term exposure to RF-EMF increases the risk of cancer, the old AD patients will have a choice between "here and now" debilitating AD or a potentially increased risk of a very rare disease - glioma (10-20 cases/100.000 people that might increase to 20-40 cases/100.000 people if the worst case scenarios from epidemiological studies ever materialized).

However, the potential risk of leakage of the blood-brain barrier should be considered as potentially very serious side effect that, unlike brain cancer, can occur rapidly (instantaneously during exposure) also in old age AD patients. If occurring, this will have serious detrimental effects on brain physiology.

Note of caution for the transgenic mice model of AD

Transgenic mice model does not reflect exactly what happens in human AD. That is why the beneficial effects of RF-EMF exposure, observed in some studies might not fully and directly apply to the human AD situation. Expression of the Tau protein, and not the decline in beta-amyloid oligomers, was recently suggested to have a larger significance in the impact of AD on human cognition.

- Is it possible that early forms of soluble amyloid aggregates (oligomers) are more toxic to neurons, before they assemble into characteristic insoluble amyloid plaques?
- Tau protein role in AD – the number of brain regions affected correlates best with cognitive decline.
- Amyloid pathology – patients with numerous beta-amyloid deposits may be cognitively normal and the beta-amyloid burden is a poor indicator of clinical disease severity in humans.
- Therefore, it is a possibility that the decline in amyloid plaques observed in transgenic AD mice, induced by the RF-EMF exposure, might have no practical impact on the AD in humans.

Summary conclusions

- Results of the experimental animal studies, including the studies in transgenic mice AD model, have produced all three possible outcomes: no effect on AD, induction of AD and prevention of AD.
- Results of the experimental in vitro studies, including the use of cells isolated from the transgenic mice AD model, have similarly produced all three possible outcomes: no effect on AD markers, induction of AD markers and prevention of AD markers. Such studies are needed to explain the possible mechanism of the AD-related effect of RF-EMF exposure. It is important to remember that the in vitro studies, especially

those showing no effect, should include positive controls to make the no-effect-result scientifically reliable.

- Contradictory observations in animal studies need to be resolved using higher numbers, than those used to date, of experimental animals.
- The potential problem of the side effects of the RF-EMF therapy for AD, such as brain cancer or leakage of the blood-brain barrier, needs to be urgently addressed because, at least in animal model, it appears that longer exposure periods are needed to elicit the anti-AD effects.
- While the brain cancer needs decades to develop and might be of not primary concern for the old age AD patients, the effects on the blood-brain barrier should be of serious concern. Human studies on BBB and RF-EMF are urgently needed because the evidence suggesting the increased leakage of the BBB caused by the RF-EMF exposures was obtained only in animal studies and is, therefore, of limited use in human situation.
- The ongoing pilot human study, executed by the Gary Arendash and co-workers, will produce, in due time, information whether long-term exposures of human brain to RF-EMF will have any impact on symptoms of the AD. Such studies are taking long time. Therefore, there is need to perform similar studies using similar experimental protocol elsewhere to produce evidence to corroborate/dismiss future observations in the Arendash's and co-workers pilot human study.
- The evidence of the preventive impact of RF-EMF exposures on the AD, obtained in transgenic mice AD model, which was replicated in at least three different laboratories, clearly indicates that the effects are of non-thermal nature. This is yet another evidence showing the existence of the non-thermal biological and health effects of the low-level RF-EMF exposures. The three sets of evidence of the existence of non-thermal effects, obtained in either human or animal studies are:
    - Human - increased risk of developing glioma (Interphone studies, Hardell studies, CERENAT study)
    - Human - effect on the sleep EEG that was replicated in Australia and Switzerland (it is unknown what is, if any, impact of this effect on human health)
    - Animal – effect of preventing/reversing AD symptoms (studies from South Korea, from Arendash and co-workers and from Banaceur and co-workers)
- The currently available scientific database on the impact of RF-EMF exposures on AD is too limited to draw any final, or far reaching, conclusions in relation to human health and human health risk.