

CELL PHONE RADIATION AND HEALTH: STRESS RESPONSE, PROTEOMICS, BLOOD-BRAIN BARRIER AND OTHER SELECTED ISSUES

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SCOPE OF THE PRESENTATION

- Presentation is not a review of the available science
- Presentation highlights some, but not all, existing gaps in the knowledge
- Presentation points out to some new potential health-related problems caused by the rapid development and broad implementation of the wireless technologies

CONTENT

- Thermal and non-thermal or just 'effects'
- Past research of my group (BioNIR & FunProt)
- Stress response
- Permeability of the blood-brain barrier (BBB)
- Leszczynski: Hypothesis linking BBB & Alzheimer's disease
- DNA damage, genotoxicity
- Sensitivity to EMF
- Game changers after 2011 IARC
- The Future: Skin & 5G technology
- Conclusions – Gaps in research

THERMAL AND NON-THERMAL OR JUST 'EFFECTS'

- Terms 'thermal' and 'non-thermal' cause confusion
- Better term: 'effects at low level exposures' = exposures at radiation levels permitted or below the current safety limits
- Effects at low level exposures = non-thermal effects
- Epidemiology and sleep EEG studies provide compelling evidence, in humans, for the existence of non-thermal effects (=low level exposure effects)
 - Epidemiology studies show effects for the regular cell phones
 - EEG shows effect, even if it is not harmful it is effect at low level exposure
 - Hypothesized that exposure heats skin and thermal receptors cause sleep EEG effect
 - Suggested that current safety limits prevent such effect
 - Claim is misleading - the sleep EEG effect occurs at the levels of RF exposure that, according to the current safety limits, should not cause any significant biological effect, neither thermal nor non-thermal

PAST RESEARCH OF MY GROUP (BioNIR & FunProt)

THE FIRST MENTION OF STRESS RESPONSE AND PROTEOMICS FROM MY RESEARCH GROUP

ABSTRACT IN *NATURE GENETICS* 2001, 27, vol. 4 supplement

Leszczynski, Dariusz

[37]

Proteomics: new way to determine possible biological effects of mobile phone radiation

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Despite years of research, the question of whether exposure to radiofrequency-modulated electromagnetic fields (RF-EMF) generated by mobile phones affects human health remains unsolved. We obtained a comprehensive overview of the possible extent of cellular response to RF-EMF irradiation by determining the total cellular changes in protein expression and in protein phosphorylation that occur in response to RF-EMF exposure under athermal conditions. As a model we used human endothelial cell line EA.hy926. Cells were exposed for one hour to a 900-MHz GSM signal. Immediately following exposure we harvested cells and extracted and separated proteins using two-dimensional electrophoresis. To determine changes in protein phosphorylation, ^{32}P was present in the cultures during the exposure period. Using Bio-Rad's PDQUEST 6.1.0 software we identified over 1,200 proteins in two-dimensional gels (10×20 cm). A large number of protein spots changed expression following irradiation. In control cells we detected over 180 phosphoproteins. RF-EMF exposure has generated a large number of newly phosphorylated proteins that were not present in controls. Among the proteins with altered phosphorylation levels were shock proteins, such as hsp27. Thus the expression and phosphorylation of a large number of proteins isolated from EA.hy926 cells seems to be altered by short RF-EMF exposure, suggesting that cells mount a vigorous response to RF-EMF stress. However, whether the observed stress can cause long-lasting physiological effects remains to be determined.

Proteomics: new way to determine possible biological effects of mobile phone radiation

“...A large number of protein spots changed expression following irradiation. In control cells we detected over 180 phosphoproteins. RF-EMF exposure has generated a large number of newly phosphorylated proteins that were not present in controls. Among the proteins with altered phosphorylation levels were shock proteins, such as hsp27. Thus the expression and phosphorylation of a large number of proteins isolated from EA.hy926 cells seems to be altered by short RF-EMF exposure, suggesting that cells mount a vigorous response to RF-EMF stress...”

PUBLICATIONS FROM MY RESEARCH GROUP

STUDIES: Stress response, Proteomics, Transcriptomics

- Leszczynski et al. Differentiation 70, 2002, 120-129
- Leszczynski et al. Proteomics 4, 2004, 426-431
- Nylund & Leszczynski. Proteomics, 4, 2004, 1359-1365
- Nylund & Leszczynski. Proteomics 6, 2006, 4769-4780
- Nylund et al. J. Proteomics & Bioinformatics 2, 2009, 455-462
- Nylund et al. Proteome Science 2010, 8:52

EFFECTS: endothelium & cell phone radiation (900 GSM at 2 W/kg)

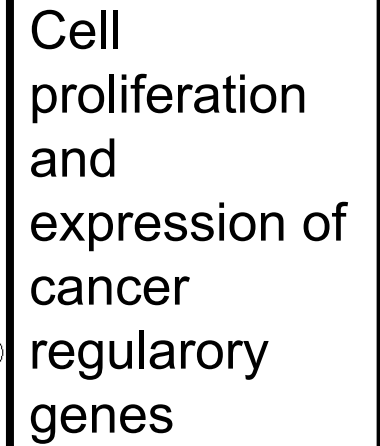
- Activates Hsp27/p38MAPK pathway in human endothelial cell lines
- Proteomics - changes in expression and phosphorylation of numerous proteins
- Transcriptomics - changes in expression of numerous genes
- Changes detected by proteomics and transcriptomics are small
- Proteome and transcriptome changes appear to be cell type-dependent

Leszczynski et al. 2002

Friedman et al. 2007

Yu et al. 2008

Lee et al. 2008



PERMEABILITY OF THE BLOOD-BRAIN BARRIER

Research studies from Salford & Persson research team

- Nittby et al. Pathophysiology. 2009, 16:103-112
- Nittby et al. Bioelectromagnetics. 2008, 29:219-232
- Belyaev et al. Bioelectromagnetics. 2006, 27:295-306
- Salford et al. Microsc Res Tech. 1994, 27:535-542

Research study from US Air Force lab

- McQuade et al. Radiation Res. 2009, 171:615-621

Research from China

- Tang et al. Brain Res. 2015, 1601:92-101

Research from Turkey

- Sirava & Seyhan. J. Chem. Neuroanatomy 2016, 75(Pt B):123-127

Research from Finland

- Leszczynski et al. Differentiation 70, 2002, 120-129

MECHANISM FOR BBB PERMEABILITY: STRESS RESPONSE

Leszczynski et al. Differentiation 70, 2002, 120-129

- Phosphorylation of Hsp27
- Phosphorylation of p38MAPK
- Activation of the p38MAPK/Hsp27 pathway
 - Weakening of cell-cell contact
 - Cell shrinking
 - Non-apoptotic cell 'blebbing'
 - Generation of growth factors

Tang et al. Brain Res. 2015, 1601:92-101

- Increased expression of mkp-1,
- De-phosphorylation of ERK
- Activation of mkp1/ERK pathway

BBB AND THE ALZHEIMER'S DISEASE

RF-EMF & AD

Table: Studies examining link between cell phone radiation and Alzheimer's disease

In vitro/In vivo	Experimental model	Exposure	Examined property	Effect	Reference
In vitro	HT22 mouse hippocampal neurons; AD model	CDMA; W-CDMA; combined 837 MHz and 1950 MHz; SAR – 2 W/kg	beta-amyloid protein-induced cytotoxicity	No effect NO	Lee JS, et al. J Radiat Res (June 20, 2016) doi: 10.1093/jrr/rnw040
In vivo	5xFAD transgenic mice – AD model	W-CDMA; 1950 MHz; SAR – 5 W/kg mean	Memory; Metabolism beta-amyloid protein	No effect NO	Son Y, et al. Bioelectromagnetics 37, 2016, 391-399
In vivo	C. elegans strain CL4176 – AD model	DECT, WiFi, GSM; 1,790–2,480 MHz	Paralysis of worm	No effect NO	Fasseas MK, et al. Int J Radiat Biol 91, 2015, 286-293
In vivo	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
In vivo	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 YES	Maaroufi K, et al. Behav Brain Res 258, 2014, 80-89
In vivo	AβPPsw+PS1 transgenic mice; AD model	GSM; 918 MHz; SAR - 0.25-1.05 W/kg	Reduction of beta-amyloid plaques	Yes effect	Arendash GW, et al. PLoS One 7, 2012, e35751
In vivo	AβPPsw+PS1 transgenic mice; AD model	GSM; 918 MHz; SAR - 0.25-1.05 W/kg	Mitochondrial function	Yes effect; enhances brain mitochondrial function YES	Dragicevic N, et al. Neuroscience 185, 2011, 135-149
In vivo	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 YES	Arendash GW, et al. J Alzheimers Dis 19, 2010, 191-210
In vitro	Rat primary cortical neurons; cholinergic SN56 cell line	GSM; 900 MHz; SAR - 1 W/kg	25-35AA beta-amyloid as RF co-stressor for oxidative damage of neural cells	Yes effect; only under particular circumstances YES	Del Vecchio G, et al. Bioelectromagnetics 30, 2009, 564-572

LESZCZYNSKI: HYPOTHESIS LINKING BBB & ALZHEIMER'S

Studies on cell phone radiation and Alzheimer's disease

- Very limited number of studies published on Alzheimer's disease (AD) and RF-EMF
- Evidence contradictory: RF-EMF has no effect on AD or RF-EMF prevents AD

Alzheimer's disease might be a by-product of immune defense

- Beta-amyloid plaques develop to trap inside bacteria and viruses – part of brain immune defense [Kumar et al. 2016]
- Development of AD might be an off-shot of the immune defense mechanism

Cell phone radiation-induced leakage of blood brain barrier

- RF-EMF has been shown to increase permeability of the BBB.
- Stress response was suggested as mechanism
 - Leszczynski et al. [2002] - p38MAPK/Hsp27
 - Tang et al. [2015] mkp-1/ERK

Leszczynski: Hypothesis linking BBB and AD

- RF-EMF-induced leakage of BBB increases influx of pathogens to brain tissue and beta-amyloid plaques are developed to entrap the pathogens
- Development of Alzheimer's might be a side effect

DNA DAMAGE, GENOTOXICITY

DNA DAMAGE, GENOTOXICITY...

- NTP study fueled debate on genotoxicity of mobile phone radiation
- Scientifically unfounded “rush to conclusions” on genotoxicity and cancer
- DNA “damage” does not automatically mean that the RF radiation is genotoxic
- DNA damage occurs also spontaneously and is repaired
- No studies to show what is the fate of the RF-induced “DNA damage”
- Is DNA damaged by RF or is RF impairing repair of spontaneous DNA damage?
- Is DNA damage repaired or does it persist in further generations of cells?
- Considering the efficiency of DNA repair mechanisms in cells, claims that mobile phone radiation is genotoxic, are not proven yet
- We do not know if mobile phone radiation exposure associated DNA damage leads to genotoxicity and mutagenicity or whether it is repaired

SENSITIVITY TO EMF

The vast majority are “feelings” studies done by psychologists

- Subjects asked how they feel and do they feel when radiation is on/off
- EHS must exist – question is only what is radiation cut-off level
- Otherwise EMF would be the only factor not causing individual sensitivity
- Problem of EHS – studied by psychologists not physiologists – wrong methods
- WHO definition of health – how to consider it? IARC classification justifies reasoning for “mental and social well-being”

Lack of studies examining biochemical responses of human tissues

- Single skin proteomics study
- Two studies examined glucose metabolism in the brain

Need for extensive human proteomics and transcriptomics studies

GAME CHANGERS AFTER 2011 IARC

Epidemiology

- Coureau G, et al. Mobile phone use and brain tumours in the CERENAT case-control study. Occup Environ Med. 2014; 71: 514-522
- Grell et al. The Intracranial Distribution of Gliomas in Relation to Exposure From Mobile Phones: Analyses From the INTERPHONE Study. Am J Epi. Nov. 2016; DOI: 10.1093/aje/kww082

Animal studies – Lerchl's group replication of Tillman et al study

- Lerchl A, et al. Tumor promotion by exposure to radiofrequency electromagnetic fields below exposure limits for humans. BBRC 2015; 459: 585-590
- Tang J, et al. Exposure to 900 MHz electromagnetic fields activates the mdk-1/ERK pathway and causes blood-brain barrier damage and cognitive impairment in rats. Brain Res. 2015; 1601: 92-101

Dosimetry – reevaluation of in vitro dosimetry by Schmid & Kuster

- Schmid G & Kuster N. The discrepancy between maximum in vitro exposure levels and realistic conservative exposure levels of mobile phones operating at 900/1800 MHz. Bioelectromagnetics. 2015; 36:133-148

THE FUTURE: SKIN & 5G TECHNOLOGY

SKIN – THE LARGEST ORGAN OF THE HUMAN BODY

- Lack of science on human skin response to RF-EMF
 - Single study on RF-EMF (GSM) and skin proteome [Karinen et al. 2008]
- 5G technology spectrum 6 GHz – 100 GHz
 - Above 6 GHz energy is deposited solely in the skin
- ICNIRP plans to classify skin as 'limbs'
 - Limbs are permitted to get higher exposure than the head and trunk

CONCLUSIONS - GAPS IN RESEARCH

Some examples (not an exhaustive list)

- Epidemiology with realistic radiation exposure data
- Search for sensitive sub-population using biochemistry methods of proteomics, transcriptomics and other 'omics' techniques
- Finding out if DNA damage happens in humans
- Examining whether human blood-brain barrier is affected
- Skin responses to 5G exposures