13. Evidence of Adverse Biological Effects of Oxidative Stress from EMF RF Radiation Exposure

13.A As in the prior evidence sections filed by Intervenor, this list of positive studies showing adverse biological effects was compiled from the AGNIR (2003 & 2012), SCENIHR (2007 & 2009) reviews and from reviews listed below. Only nine (9), marked with an*, of the fifty five eight (55) positive studies listed below have been included by AGNIR or SCENIHR in their reviews of the evidence for biological effects of EMF radiation on this topic, even though many of the studies were published during the same time period covered by their reviews.

1. Avci B, Akar A, Bilgici B, Tuncel OK. *Oxidative stress induced by 1.8 GHz radio frequency electromagnetic radiation and effects of garlic extract in rats.* Int J Rad Biol 2012;88:799-805. http://www.ncbi.nlm.nih.gov/pubmed/22788526 Abstract: PURPOSE: We aimed to study the oxidative damage induced by radiofrequency electromagnetic radiation (RF-EMR) emitted by mobile telephones and the protective effect of garlic extract used as an anti-oxidant against this damage. MATERIALS AND METHODS: A total of 66 albino Wistar rats were divided into three groups. The first group of rats was given 1.8 GHz, 0.4 W/kg specific absorption rate (SAR) for 1 h a day for three weeks. The second group was given 500 mg/kg garlic extract in addition to RF-EMR. The third group of rats was used as the control group. At the end of the study, blood and brain tissue samples were collected from the rats. RESULTS: After the RF-EMR exposed, the advanced oxidation protein product (AOPP) levels of brain tissue increased compared with the control group (p < 0.001). Garlic administration accompanying the RF-EMR, on the other hand, significantly reduced AOPP levels in brain tissue (p < 0.001). The serum nitric oxide (NO) levels significantly increased both in the first and second group (p < 0.001). However, in the group for which garlic administration accompanied that of RF-EMR, there was no difference in serum NO levels compared with the RF-EMR exposed group (p > 0.05). There was no significant difference among the groups with respect to malondialdehyde (MDA) levels in brain tissue and blood samples (p > 0.05). Similarly, no difference was detected among the groups regarding serum paroxonase (PON) levels (p > 0.05). We did not detect any PON levels in the brain tissue. CONCLUSIONS: The exposure of RF-EMR similar to 1.8 GHz Global system for mobile communication (GSM) leads to protein oxidation in brain tissue and an increase in serum NO. We observed that garlic administration reduced protein oxidation in brain tissue and that it did not have any effects on serum NO levels.

human endothelial cell lines showed that exposure to RF-EMF changed the expression and phosphorylation of numerous, largely unidentified proteins. Among these proteins is the heat shock protein hsp27, a marker for cellular stress responses. There was no evidence that RF-EMF affected processes such as cell proliferation, apoptosis or immune cell functionality. For both ELF-EMF and RF-EMF, the results of the whole genome cDNA micro-array and proteomic analyses indicated that EMF may activate several groups of genes that play a role in cell division, cell proliferation and cell differentiation. At present the biological relevance of these findings cannot be assessed.

Abstract: PURPOSE: To investigate the effects of mobile-phone-emitted radiation on the oxidant/antioxidant balance in corneal and lens tissues and to observe any protective effects of vitamin C in this setting. CONCLUSIONS: The results of this study suggest that mobile telephone radiation leads to oxidative stress in corneal and lens tissues and that antioxidants such as vitamin C can help to prevent these effects.

4. Blank M. A Rationale for a Biologically-based Public Exposure Standard for Electromagnetic Fields (ELF and RF) Section 7 - The Cellular Stress Response: EMF-DNA Interaction, 2012 Supplement. BioInitiative Working Group, BioInitiative Report, 2012. Review [Copy filed in Docket] Excerpt: The transition from heat shock protein to stress protein should alert (perhaps even alarm) the government agencies responsible for setting EMF safety standards. The thermal stimuli that evoked synthesis of protective proteins were believed to be dangerous for cells, but now we see that non-thermal EMF stimuli cause the same protective reactions in cells. The heat shock response and the EMF stress response both relate to the threshold for biological damage, and we should realize that EMF damage is caused by non-thermal stimuli. Compared to the energy needed to stimulate heat shock, EMF requires but a small fraction of the thermal energy needed to produce the same response (Blank et al., 1992).
Excerpt (pg. 16): Research has shown that the EMF-activated cellular stress response: is an effective protective mechanism for cells exposed to a wide range of EMF frequencies - thresholds are very low (safety standards must be reduced to limit biological responses) -mechanism involves direct interaction of EMF with the DNA molecule (claims that there are no known mechanisms of interaction are patently false) - the coiled-coil structure of DNA in the nucleus makes the molecule react like a fractal antenna to a wide range of frequencies (there is a need for stricter EMF safety standards) -biologically-based EMF safety standards could be developed from the research on the stress response.

5. Blank M, Goodman R. DNA is a fractal antenna in electromagnetic fields. Int J Radiat Biol. 2011 Apr;87(4):409-15. Abstract: PURPOSE: To review the responses of deoxyribonucleic acid (DNA) to electromagnetic fields (EMF) in different frequency ranges, and characterize the properties of DNA as an antenna. RESULTS: EMF interactions with DNA are similar over a range of non-ionizing frequencies, i.e., extremely low frequency (ELF) and radio frequency (RF) ranges. There are similar effects in the ionizing range, but the reactions are more complex. CONCLUSIONS: The wide frequency range of interaction with EMF is the functional characteristic of a fractal antenna, and DNA appears to possess the two structural characteristics of fractal antennas, electronic conduction and self symmetry. These properties contribute to greater reactivity of DNA with EMF in the environment, and the DNA damage could account for increases in cancer epidemiology, as well as variations in the rate of chemical evolution in early geologic history.

response genes, e.g., HSP70, and increased levels of stress proteins, e.g., hsp70. The 20 different stress protein families are evolutionarily conserved and act as 'chaperones' in the cell when they 'help' repair and refold damaged proteins and transport them across cell membranes. Induction of the stress response involves activation of DNA, and despite the large difference in energy between ELF and RF, the same cellular pathways respond in both frequency ranges. Specific DNA sequences on the promoter of the HSP70 stress gene are responsive to EMF, and studies with model biochemical systems suggest that EMF could interact directly with electrons in DNA. While low energy EMF interacts with DNA to induce the stress response, increasing EMF energy in the RF range can lead to breaks in DNA strands. It is clear that in order to protect living cells, EMF safety limits must be changed from the current thermal standard, based on energy, to one based on biological responses that occur long before the threshold for thermal changes.

7. Blank M. Protein and DNA reactions stimulated by electromagnetic fields. Electromagnetic Biology and Medicine 2008, 27: 3-23. Review [http://www.ncbi.nlm.nih.gov/pubmed/18327711 Abstract: The stimulation of protein and DNA by electromagnetic fields (EMF) has been problematic because the fields do not appear to have sufficient energy to directly affect such large molecules. Studies with electric and magnetic fields in the extremely low-frequency range have shown that weak fields can cause charge movement. It has also been known for some time that redistribution of charges in large molecules can trigger conformational changes that are driven by large hydration energies. This review considers examples of direct effects of electric and magnetic fields on charge transfer, and structural changes driven by such changes. Conformational changes that arise from alterations in charge distribution play a key role in membrane transport proteins, including ion channels, and probably account for DNA stimulation to initiate protein synthesis. It appears likely that weak EMF can control and amplify biological processes through their effects on charge distribution.

8. Blank M. A Scientific Perspective on Health Risk of Electromagnetic Fields: Section 7- Evidence for Stress Response (Stress Proteins). BioInitiative Working Group, BioInitiative Report, 2007. Review [Copy filed in Docket] Excerpt (pg. 3 ): The stress response is a protective cellular mechanism that is characterized by stress protein synthesis. The stress response, by its very nature, shows that cells react to EMFs as potentially harmful. The stress response is an important protective mechanism that enables cells from animals, plants and bacteria to survive environmental stressors with the aid of heat shock proteins (hsp). It is stimulated by both non-thermal power (ELF), and non-thermal radiofrequency (RF) as well as thermal radio (RF) frequency EMFs, so the greatly differing energies are not critical in activating the DNA to synthesize proteins. Fewer than one quarter of the relevant references listed in Table 1 appear in the IEEE list leading to the newly revised IEEE C95.1 recommendations (April, 2006). Excerpt (pg. 22-23 ): The response involves activation of DNA, i.e., stimulating stress genes as well as genes that sense and repair damage to DNA and proteins. Scientific research has identified specific segments of DNA that respond to EMF and it has been possible to move these specific segments of DNA and transfer the sensitivity to EMF. At high EMF intensities, the interaction with DNA can lead to DNA strand breaks that could result in mutation, an initiating step in the development of cancer. Scientific research has shown that ELF/RF interact with DNA to stimulate protein synthesis, and at higher intensities to cause DNA damage. Regarding EMF mechanisms, we still have much to learn, but we know that the energy and field strength thresholds of many biological reactions are very low (Table 2). These findings indicate that safe exposure levels for the public should be substantially lowered, if only as a precautionary measure. Even when stated in vague terms, so as to require little more than lip service, a precautionary policy has not yet been recommended by the WHO. Excerpt (pg. 10): Regarding EMF mechanisms, we still have much to learn, but we know that the energy and field strength thresholds of many biological reactions are very low (Table 2). These findings indicate that safe exposure levels for the public should be substantially lowered, if only as a precautionary measure. Even when stated in vague terms, so as to require little more than lip service, a precautionary policy has not
yet been recommended by the WHO. Thus, the two main problems of research on EMF risk, defining a biological dose and the desired level of exposure protection, remain to be solved.

9. *Bohr H, Bohr J. Microwave enhanced kinetics observed in ORD studies of protein. Bioelectromagnetics. 2000 21:68-72. http://www.ncbi.nlm.nih.gov/pubmed/10615094 Abstract: Microwaves are shown to affect the kinetics of conformational changes of the protein beta-lactoglobulin. Microwaves can accelerate conformational changes in the direction towards the equilibrium state. This applies both for the folding and the unfolding processes. Cold denaturing thermal unfolding of the proteins is accelerated by negative temperature gradients. Microwave irradiation of the protein solution heated it by about 0.3 degree, and hence the observed acceleration of denaturing is therefore non-thermal.

10. Ceyhan AM, Akkaya VB, Güleçol ŞC, Ceyhan BM, Ö zgüner F, Chen W. Protective effects of β-glucan against oxidative injury induced by 2.45-GHz electromagnetic radiation in the skin tissue of rats. Arch Dermatol Res. 2012 Sep;304(7):521-7. http://www.ncbi.nlm.nih.gov/pubmed/22237725 Abstract: In recent times, there is widespread use of 2.45-GHz irradiation-emitting devices in industrial, medical, military and domestic application. The aim of the present study was to investigate the effect of 2.45-GHz electromagnetic radiation (EMR) on the oxidant and antioxidant status of skin and to examine the possible protective effects of β-glucans against the oxidative injury. Thirty-two male Wistar albino rats were randomly divided into four equal groups: control; sham exposed; EMR; and EMR + β-glucan. A 2.45-GHz EMR emitted device from the experimental exposure was applied to the EMR group and EMR + β-glucan group for 60 min daily, respectively, for 4 weeks. β-glucan was administered via gavage at a dose of 50 mg/kg/day before each exposure to radiation in the treatment group. The activities of antioxidant enzymes, superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase (CAT), as well as the concentration of malondialdehyde (MDA) were measured in tissue homogenates of the skin. Exposure to 2.45-GHz EMR caused a significant increase in MDA levels and CAT activity, while the activities of SOD and GSH-Px decreased in skin tissues. Systemic β-glucan significantly reversed the elevation of MDA levels and the reduction of SOD activities. β-glucan treatment also slightly enhanced the activity of CAT and prevented the depletion of GSH-Px activity caused by EMR, but not statistically significantly. The present study demonstrated the role of oxidative mechanisms in EMR-induced skin tissue damages and that β-glucan could ameliorate oxidative skin injury via its antioxidant properties.

11. *Czyz J, Guan K, Zeng Q, Nikolova T, Meister A, Schönborn F, Schüderer I, Kuster N, Wobus AM. 2004. High frequency electromagnetic fields (GSM signals. affect gene expression levels in tumor suppressor p53-deficient embryonic stem cells. Bioelectromagnetics 25: 296-307. http://www.ncbi.nlm.nih.gov/pubmed/15114639 Abstract: Effects of electromagnetic fields (EMF) simulating exposure to the Global System for Mobile Communications (GSM) signals were studied using pluripotent embryonic stem (ES) cells in vitro. Wild-type ES cells and ES cells deficient for the tumor suppressor p53 were exposed to pulse modulated EMF at 1.71 GHz, lower end of the uplink band of GSM 1800, under standardized and controlled conditions, and transcripts of regulatory genes were analyzed during in vitro differentiation. Two dominant GSM modulation schemes (GSM-217 and GSM-Talk), which generate temporal changes between GSM-Basic (active during talking phases) and GSM-DTX (active during listening phases thus simulating a typical conversation), were applied to the cells at and below the basic safety limits for local exposures as defined for the general public by the International Commission on Nonionizing Radiation Protection (ICNIRP). GSM-217 EMF induced a significant upregulation of mRNA levels of the heat shock protein, hsp70 of p53-deficient ES cells differentiating in vitro, paralleled by a low and transient increase of c-jun, c-myc, and p21 levels in p53-deficient, but not in wild-type cells. No responses were observed in either cell type after EMF exposure to GSM-Talk applied at similar slot-averaged specific absorption rates (SAR), but at lower time-
averaged SAR values. Cardiac differentiation and cell cycle characteristics were not affected in embryonic stem and embryonic carcinoma cells after exposure to GSM-217 EMF signals. Our data indicate that the genetic background determines cellular responses to GSM modulated EMF. Bioelectromagnetics 25:296-307, 2004.

*Abstract:* Exposure to microwave radiation enhances the aggregation of bovine serum albumin in vitro in a time- and temperature-dependent manner. Microwave radiation also promotes amyloid fibril formation by bovine insulin at 60 degrees C. These alterations in protein conformation are not accompanied by measurable temperature changes, consistent with estimates from field modelling of the specific absorbed radiation (15-20 mW kg(-1)). Limited denaturation of cellular proteins could explain our previous observation that modest heat-shock responses are induced by microwave exposure in Caenorhabditis elegans. We also show that heat-shock responses both to heat and microwaves are suppressed after RNA interference ablating heat-shock factor function.

*Excerpt:* Conclusion: We have reviewed the literature to better understand the effects of cell phone radiation on human health, especially on fertility and in relation to cancer. Commercially available cellular phones might affect cell function via non-thermal effects. We hypothesized that the plasma membrane might be the target of cell phone radiation. RF-EMW can increase ROS formation by increasing the activity of plasma membrane NADH oxidase. *Prolonged exposure to RF-EMW can also cause DNA damage (by prolonged OS), which may accelerates neuronal and spermatozoal cell death and promote neurodegenerative processes as well as promote brain and testicular carcinogenesis.* Any tumor promoting effects of RF-EMW might be due to the effect it has on PKC, ODC, intra cellular calcium spikes and stimulation of stress kinase. Stimulation of plasma membrane NADH oxidase might play central role in above mentioned effects. OS and changes in PKC activity might lead to the RF-EMW related infertility observed in numerous studies. Hence, RF-EMW from commercially available cell phones might affect the fertilizing potential of spermatozoa. Therefore, the SAR limit (maximum acceptable exposure limit) should be lowered for cellular phones. However, more studies are necessary to provide definitive evidence against cell phone radiation, which can be provided by in vitro studies combined with computational biomodeling.

*Abstract:* In this study, the aim was to investigate possible effects of Electromagnetic Radiation (EMR) use on oxidant and antioxidant status in erythrocytes and kidney, heart, liver, and ovary tissues from rats, and possible protective role of vitamin C. For this aim, 40 Wistar albino female rats were used throughout the study. The treatment group was exposed to EMR in a frequency of 900 MHz, the EMR plus vitamin C group was exposed to the same EMR frequency and given vitamin C (250 mg/kg/day) orally for 4 weeks. There were 10 animals in each group including control and vitamin C groups. At the end of the study period, blood samples were obtained from the animals to get erythrocyte sediments. Then the animals were sacrificed and heart, kidney, liver, and ovary tissues were removed. Malondialdehyde (MDA) levels and superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), xanthine oxidase (XO), and adenosine deaminase (ADA) enzyme activities were measured in the tissues and erythrocytes. It was
observed that MDA level, XO, and GSH-Px activities significantly increased in the EMR group as compared with those of the control group in the erythrocytes. In the kidney tissues, it was found that MDA level and CAT activity significantly increased, whereas XO and ADA activities decreased in the cellular phone group as compared with those of the control group. However, in the heart tissues it was observed that MDA level, ADA, and XO activities significantly decreased in the cellular phone group as compared with those of the control group. The results suggest that EMR at the frequency generated by a cell phone causes oxidative stress and peroxidation in the erythrocytes and kidney tissues from rats. In the erythrocytes, vitamin C seems to make partial protection against the oxidant stress.

15. Elhag MA, Nabil GM, Attia AMM. Effects of electromagnetic field produced by mobile phones on the oxidant and antioxidant status of rats. Pak J Biol Sc 2007; 10: 4271-4. http://www.ncbi.nlm.nih.gov/pubmed/19086584 Abstract: This study was designed to investigate the effect of EMR produced by GSM Mobile Phones (MP) on the oxidant and antioxidant status in rats. Rats were divided into three groups: (1) controls, (2) rats exposed to a fractionated dose of EMR (15 min day(-1) for four days) (EMR-F) and (3) rats exposed to an acute dose of EMR (EMR-A). A net drop in the plasma concentration of vitamin C (-47 and -59.8%) was observed in EMR-F and EMR-A groups, respectively, when compared to controls. While, a significant decrease in the levels of lipophilic antioxidant vitamins: vitamin E (-33 and -65.8%), vitamin A (-44.4 and -46.8%) was observed in EMR-F and EMR-A groups, respectively, when compared to controls. A net drop in plasma level of reduced glutathione (GSH) (-19.8 and -35.3%) was observed in EMR-F and EMR-A groups, respectively. EMR exposure of rats produced a significant decrease in catalase (CAT) and superoxide dismutase (SOD) activities, with the values of these activities for EMR-A group is significantly lower than those of EMR-F. These results indicate that the effects of acute doses of EMR produced by mobile phones on the rat's antioxidant status is significantly higher than those of fractionated doses of the same type of radiation. On the basis of present results, it can be concluded that exposure to acute doses of EMR produced by mobile phones is more hazardous than that produced by fractionated doses of the same type of radiation.

16. Eşmekaya MA, Çiğdem Özer, Nesrin Seyhan (2011). Effects of 900 MHz Pulse Modulated Radiofrequency Radiation on Heart, Lung, Testis and Liver tissues Oxidant and Antioxidant Levels. General Physiology and Biophysics, 30(84-89). http://www.ncbi.nlm.nih.gov/pubmed/21460416 Abstract: Oxidative stress may affect many cellular and physiological processes including gene expression, cell growth, and cell death. In the recent study, we aimed to investigate whether 900 MHz pulse-modulated radiofrequency (RF) fields induce oxidative damage on lung, heart and liver tissues. We assessed oxidative damage by investigating lipid peroxidation (malondialdehyde, MDA), nitric oxide (NOx) and glutathione (GSH) levels which are the indicators of tissue toxicity. A total of 30 male Wistar albino rats were used in this study. Rats were divided randomly into three groups; control group (n = 10), sham group (device off, n = 10) and 900 MHz pulsed-modulated RF radiation group (n = 10). The RF rats were exposed to 900 MHz pulsed modulated RF radiation at a specific absorption rate (SAR) level of 1.20 W/kg 20 min/day for three weeks. MDA and NOx levels were increased significantly in liver, lung, testis and heart tissues of the exposed group compared to sham and control groups (p < 0.05). Conversely GSH levels were significantly lower in exposed rat tissues (p < 0.05). No significantly difference was observed between sham and control groups. Results of our study showed that pulse-modulated RF radiation causes oxidative injury in liver, lung, testis and heart tissues mediated by lipid peroxidation, increased level of NOx and suppression of antioxidant defense mechanism.

In brief, EMF exposure has been shown to cause high oxidative stress-induced biological damage, manifested by a substantial increase of peroxidized lipids, oxidized proteins and fragmented/nicked DNA. Substantial decrease has been also documented in the antioxidant defense mechanisms, i.e., in the activity of crucial antioxidant enzymes and in the concentration of endogenous antioxidants. Exogenous antioxidants and inhibitors of certain ROS/RNS-producing enzymes reversed all these effects, which is another strong evidence for the causative relation between oxidative stress and EMF exposure. EMF-induced oxidative stress has been also shown in vitro by the increase of reactive oxygen/nitrogen species (ROS/RNS) indirectly assessed by non-specific assays. New quantitative and specific in vivo ROS assays are proposed for the conclusive verification of the oxidative stress mechanism, as well as specific quantitative indicators of biological damage that can be used for the reassessment of the EMF exposure limits. The present report offers a combined free radical pair/oxidative stress mechanism in order to explain how EMFs can cause disease in man. Moreover, it offers a scientifically solid background mechanism for the experimental design of epidemiological studies, while it extends its conclusions to the redefinition of safer EMF exposure limits for the public.


Abstract: The question of how electromagnetic fields--static or low to high frequency--interact with biological systems is of great interest. The current discussion among biologists, chemists, and physicists emphasizes aspects of experimental verification and of defining microscopic and macroscopic mechanisms. Both aspects are reviewed here. We emphasize that in certain situations nonthermal interactions of electromagnetic fields occur with cellular systems.


Abstract: The levels of blood lipid peroxidation, glutathione peroxidase, reduced glutathione, and vitamin C were used to follow the level of oxidative damage caused by 2.45 GHz electromagnetic radiation in rats. The possible protective effects of selenium and L-carnitine were also tested and compared to untreated controls. Thirty male Wistar Albino rats were equally divided into five groups, namely Groups A1 and A2: controls and sham controls, respectively; Group B: EMR; Group C: EMR + selenium, Group D: EMR + L-carnitine. Groups B–D were exposed to 2.45 GHz electromagnetic radiation during 60 min/day for 28 days. The lipid peroxidation levels in plasma and erythrocytes were significantly higher in group B than in groups A1 and A2 (p<0.05), although the reduced glutathione and glutathione peroxidase values were slightly lower in erythrocytes of group B compared to groups A1 and A2. The plasma lipid peroxidation level in group A2 was significantly lower than in group B (p<0.05). Erythrocyte reduced glutathione levels (p<0.01) in group B; erythrocyte glutathione peroxidase activity in group A2 (p<0.05), group B (p<0.001), and group C (p<0.05) were found to be lower than in group D. In conclusion, 2.45 GHz electromagnetic radiation caused oxidative stress in blood of rat. L-carnitine seems to have protective effects on the 2.45-GHz-induced blood toxicity by inhibiting free radical supporting antioxidant redox system although selenium has no effect on the investigated values.


Abstract: There are numerous reports on the effects of electromagnetic radiation (EMR) in various cellular systems. Mechanisms of adverse effects of EMR indicate that reactive oxygen species (ROS) may play a role in the biological effects of this radiation. The aims of this study were to examine 900 MHz mobile phone-induced oxidative stress that promotes production of ROS and to investigate the role...
of vitamins E and C, which have antioxidant properties, on endometrial tissue against possible 900 MHz mobile phone-induced endometrial impairment in rats. The animals were randomly grouped (eight each) as follows: 1) Control group (without stress and EMR, Group I), 2) sham-operated rats stayed without exposure to EMR (exposure device off, Group II), 3) rats exposed to 900 MHz EMR (EMR group, Group III) and 4) a 900 MHz EMR exposed + vitamin-treated group (EMR + Vit group, Group IV). A 900 MHz EMR was applied to EMR and EMR + Vit group 30 min/day, for 30 days using an experimental exposure device. Endometrial levels of nitric oxide (NO, an oxidant product) and malondialdehyde (MDA, an index of lipid peroxidation), increased in EMR exposed rats while the combined vitamins E and C caused a significant reduction in the levels of NO and MDA. Likewise, endometrial superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) activities decreased in EMR exposed animals while vitamins E and C caused a significant increase in the activities of these antioxidant enzymes. In the EMR group histopathologic changes in endometrium, diffuse and severe apoptosis was present in the endometrial surface epithelial and glandular cells and the stromal cells. Diffuse eosinophilic leucocyte and lymphocyte infiltration were observed in the endometrial stroma whereas the combination of vitamins E and C caused a significant decrease in these effects of EMR. It is concluded that oxidative endometrial damage plays an important role in the 900 MHz mobile phone-induced endometrial impairment and the modulation of oxidative stress with vitamins E and C reduces the 900 MHz mobile phone-induced endometrial damage both at biochemical and histological levels.

21. Harvey C, French PW. Effects on protein kinase C and gene expression in a human mast cell line, HMC-1, following microwave exposure. Cell Biol Int. 2000 23:739-748. http://www.ncbi.nlm.nih.gov/pubmed/10736198 Abstract: We used a resonant cavity which delivered a continuous wave exposure at 864.3 MHz at an average specific absorption rate (SAR) of 7 W/kg to determine non-thermal biological effects of microwave exposure. A human mast cell line, HMC-1, was used as the biological target. Cells were given three exposures each of 20-min duration daily for 7 days. The temperature of the cell culture medium during the exposure fell to 26.5 degrees C. Effects were seen on localization of protein kinase C, and expression of three genes of 588 screened. The affected genes included the proto-oncogene c-kit, the transcription factor Nucleoside diphosphate kinase B and the apoptosis-associated gene DAD-1. Stress response genes were variably upregulated. No significant effect on morphology or on F-actin distribution was detected. We conclude that low-power microwave exposure may act on HMC-1 cells by altering gene expression via a mechanism involving activation of protein kinase C, and at temperatures well below those known to induce a heat shock response.

22. Irmak MK, Fadillioglu E, Gulec M, et al. Effects of electromagnetic radiation from a cellular telephone on the oxidant and antioxidant levels in rabbits. Cell Biochem Funct 2002; 20: 279-83. http://www.ncbi.nlm.nih.gov/pubmed/12415560 Abstract: The number of reports on the effects induced by electromagnetic radiation (EMR) in various cellular systems is still increasing. Until now no satisfactory mechanism has been proposed to explain the biological effects of this radiation. Oxygen free radicals may play a role in mechanisms of adverse effects of EMR. This study was undertaken to investigate the influence of electromagnetic radiation of a digital GSM mobile telephone (900 MHz) on oxidant and antioxidant levels in rabbits. Adenosine deaminase, xanthine oxidase, catalase, myeloperoxidase, superoxide dismutase (SOD) and glutathione peroxidase activities as well as nitric oxide (NO) and malondialdehyde levels were measured in sera and brains of EMR-exposed and sham-exposed rabbits. Serum SOD activity increased, and serum NO levels decreased in EMR-exposed animals compared to the sham group. Other parameters were not changed in either group. This finding may indicate the possible role of increased oxidative stress in the pathophysiology of adverse effect of EMR. Decreased NO levels may also suggest a probable role of NO in the adverse effect.

**Abstract:** BACKGROUND: The widespread use of mobile phones (MP) in recent years has raised the research activities in many countries to determine the consequences of exposure to the low-intensity electromagnetic radiation (EMR) of mobile phones. Since several experimental studies suggest a role of reactive oxygen species (ROS) in EMR-induced oxidative damage in tissues, in this study, we investigated the effect of Ginkgo biloba (Gb) on MP-induced oxidative damage in brain tissue of rats. METHODS: Rats (EMR+) were exposed to 900 MHz EMR from MP for 7 days (1 h/day). In the EMR+Gb groups, rats were exposed to EMR and pretreated with Gb. Control and Gb-administrated groups were produced by turning off the mobile phone while the animals were in the same exposure conditions. Subsequently, oxidative stress markers and pathological changes in brain tissue were examined for each groups. RESULTS: Oxidative damage was evident by the: (i) increase in malondialdehyde (MDA) and nitric oxide (NO) levels in brain tissue, (ii) decrease in brain superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activities and (iii) increase in brain xanthine oxidase (XO) and adenosine deaminase (ADA) activities. These alterations were prevented by Gb treatment. Furthermore, Gb prevented the MP-induced cellular injury in brain tissue histopathologically. CONCLUSION: Reactive oxygen species may play a role in the mechanism that has been proposed to explain the biological side effects of MP, and Gb prevents the MP-induced oxidative stress to preserve antioxidant enzymes activity in brain tissue.


**Abstract:** In this study, we aimed to investigate the possible protective effects of caffeic acid phenethyl ester (CAPE) on lipid peroxidation (LPO) and the activities of antioxidant enzymes in the liver of rats exposed to the 900 MHz electromagnetic field (EMF). EMF of cellular phones may affect biological systems by increasing free radical, which appear mainly to enhance LPO, and by changing the antioxidative activities of liver, thus leading to oxidative damage. CAPE, an active component of propolis extract, exhibits antioxidative properties and several studies suggest that supplementation with antioxidant can influence EMF exposure induced hepatotoxicity. Thirty male Sprague-Dawley rats were divided into three groups: control (n = 10), 900 MHz EMF (n = 10) and 900 MHz EMF + CAPE (n = 10). CAPE was injected intraperitoneally for 30 days before exposure to EMF. Liver tissue was removed to study the activities of catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), xanthine oxidase (XO) and the levels of LPO. The activities of XO, CAT and level of LPO increased in the 900 MHz electromagnetic field (EMF) group compared with the control group, although XO, CAT activities and LPO levels were decreased by 900 MHz EMF + CAPE administration. The activities of SOD and GSH-Px decreased in the 900 MHz EMF group compared with the control group, although their levels were increased by EMF + CAPE administration. It can be concluded that CAPE may prevent the 900 MHz EMF-induced oxidative changes in liver by strengthening the antioxidant defense system by reducing reactive oxygen species and increasing antioxidant enzyme activities.


**Abstract:** We investigated the effects of green tea catechin on oxidative damage in microwave-exposed rats. The microwave-exposed rats received one of three diets: catechin-free (MW-0C), 0.25% catechin (MW-0.25C), or 0.5% catechin (MW-0.5C). Rats were sacrificed 6 days after microwave irradiation (2.45 GHz, 15 minutes). Cytochrome P(450) levels in the MW-0C group was increased by 85% compared
with normal, but was 11% and 14% lower in the MW-0.25C and MW-0.5C groups than in the MW-0C group. NADPH-cytochrome P(450) reductase activity in the MW-0C group was increased by 29%, compared with the normal group, but was significantly less in the MW-0.25C and MW-0.5C groups. Superoxide dismutase activity in the MW-0C group was decreased by 34%, compared with the normal group, but in the MW-0.25C and MW-0.5C groups was 19% and 25% higher. The activity of glutathione peroxidase in the MW-0C group was decreased by 28% but remained near normal with catechin supplements. Superoxide radical concentrations in the MW-0C group were increased by 35%, compared with the normal group. However, superoxide radicals in the MW-0.25C and MW-0.5C groups were 11% and 12% lower, respectively, compared with the MW-0C group. Microwave irradiation significantly increased levels of thiobarbituric acid-reactive substances, carbonyl values, and lipofuscin contents, but green tea catechin partially overcame the effects of the microwave irradiation. In conclusion, the mixed function oxidase system was activated, the formation of superoxide radical, lipid peroxide, oxidized protein, and lipofuscin was increased, and the antioxidative defense system was weakened in heart tissue of microwave-exposed rats, but the oxidative damage was significantly reduced by catechin supplementation.


Abstract: The biological effect of radiofrequency (RF) fields remains controversial. We address this issue by examining whether RF fields can cause changes in gene expression. We used the pulsed RF fields at a frequency of 2.45 GHz that is commonly used in telecommunication to expose cultured human HL-60 cells. We used the serial analysis of gene expression (SAGE) method to measure the RF effect on gene expression at the genome level. We observed that 221 genes altered their expression after a 2-h exposure. The number of affected genes increased to 759 after a 6-h exposure. Functional classification of the affected genes reveals that apoptosis-related genes were among the upregulated ones and the cell cycle genes among the downregulated ones. We observed no significant increase in the expression of heat shock genes. These results indicate that the RF fields at 2.45 GHz can alter gene expression in cultured human cells through non-thermal mechanism.

Abstract: We have examined whether non-thermal exposures of cultures of the human endothelial cell line EA.hy926 to 900 MHz GSM mobile phone microwave radiation could activate stress response. Results obtained demonstrate that 1-hour non-thermal exposure of EA.hy926 cells changes the phosphorylation status of numerous, yet largely unidentified, proteins. One of the affected proteins was identified as heat shock protein-27 (hsp27). Mobile phone exposure caused a transient increase in phosphorylation of hsp27, an effect which was prevented by SB203580, a specific inhibitor of p38 mitogen-activated protein kinase (p38MAPK). Also, mobile phone exposure caused transient changes in the protein expression levels of hsp27 and p38MAPK. All these changes were non-thermal effects because, as determined using temperature probes, irradiation did not alter the temperature of cell cultures, which remained throughout the irradiation period at 37 +/- 0.3 degrees C. Changes in the overall pattern of protein phosphorylation suggest that mobile phone radiation activates a variety of cellular signal transduction pathways, among them the hsp27/p38MAPK stress response pathway. Based on the known functions of hsp27, we put forward the hypothesis that mobile phone radiation-induced activation of hsp27 may (i) facilitate the
development of brain cancer by inhibiting the cytochrome c/caspase-3 apoptotic pathway and (ii) cause an increase in blood-brain barrier permeability through stabilization of endothelial cell stress fibers. We postulate that these events, when occurring repeatedly over a long period of time, might become a health hazard because of the possible accumulation of brain tissue damage. Furthermore, our hypothesis suggests that other brain damaging factors may co-participate in mobile phone radiation-induced effects.

30. Liu C, Duan W, Xu S, Chen C, He M, Zhang L, Yu Z, Zhou Z. Exposure to 1800MHz radiofrequency electromagnetic radiation induces oxidative DNA base damage in a mouse spermatocyte-derived cell line. Toxicology Letters 2013; 1800MHz Global System for Mobile Communication (GSM) signals in GSM-Talk mode at specific absorption rates (SAR) of 1W/kg, 2W/kg or 4W/kg. Subsequently, through the use of formamidopyrimidine DNA glycosylase (FPG) in a modified comet assay, we determined that the extent of DNA migration was significantly increased at a SAR of 4W/kg. Flow cytometry analysis demonstrated that levels of the DNA adduct 8-oxoguanine (8-oxoG) were also increased at a SAR of 4W/kg. These increases were concomitant with similar increases in the generation of reactive oxygen species (ROS); these phenomena were mitigated by co-treatment with the antioxidant \( \alpha \)-tocopherol. However, no detectable DNA strand breakage was observed by the alkaline comet assay. Taking together, these findings may imply the novel possibility that RF-EMR with insufficient energy for the direct induction of DNA strand breaks may produce genotoxicity through oxidative DNA base damage in male germ cells.

Abstract: We investigated c-myc protein-binding sites on the HSP70 promoter as modulators of the induction of HSP70 gene expression in response to magnetic field stimulation (8microT at 60Hz) and whether the presence of c-myc protein potentiates transactivation of HSP70 expression. A 320 base pair region in the HSP70 promoter (+1 to -320) was analyzed. This region contains two c-myc-protein binding sites with consensus sequences located at -230 and -160 nucleotide positions (relative to the transcription initiation site) and overlapping with the region reported for the regulation of HSP70 gene expression by c-myc protein. This promoter region is upstream of other regulatory sequences, including the heat shock element (HSE), AP-2, and serum response element (SRE). Transfectants containing both c-myc protein-binding sites, HSP-MYC A and HSP-MYC B, and exposed to magnetic fields showed a 3.0-fold increase in expression of CAT activity as compared with sham-exposed control transfectants. Transfectants containing one c-myc binding site, HSP-MYC A, and exposed to magnetic fields showed a 2.3-fold increase in CAT expression. Transfectants in which both HSP-MYC A and HSP-MYC B binding sites were deleted showed no magnetic field sensitivity; values were virtually identical with sham-exposed controls. If the c-myc expression vector was not co-transfected with the constructs containing myc-binding sites, there was no difference in the expression of CAT activity between magnetically stimulated and sham-exposed controls, although both responded to heat shock. These data suggest that endogenous elevated levels of myc protein contribute to the induction of HSP70 in response to magnetic field stimulation.

Abstract: HSP70 gene expression is induced by a wide range of environmental stimuli, including 60-Hz electromagnetic fields. In an earlier report we showed that the induction of HSP70 gene expression by magnetic fields is effected at the level of transcription and is mediated through c-myc protein binding at two nCTCTn sequences at -230 and -160 in the
human HSP70 promoter. We report on the identification of a third c-myc binding site (between -158 and -162) that is an important regulator of magnetic field-induced HSP70 expression. We also show that the heat shock element (HSE), lying between -180 and -203, is required for induction of HSP70 gene expression by magnetic fields. The HSE centered at -100 alone is insufficient.

33. Lin H, Blank M, Rossol-Haseroth K, Goodman R. 2001. *Regulating genes with electromagnetic response elements.* Journal of Cellular Biochemistry 81:143-148. [http://www.ncbi.nlm.nih.gov/pubmed/11180404](http://www.ncbi.nlm.nih.gov/pubmed/11180404) **Abstract:** A 900 base pair segment of the c-myc promoter, containing eight nCTCTn sequences, is required for the induction of c-myc expression by electromagnetic (EM) fields. Similarly, a 70 bp region of the HSP70 promoter, containing three nCTCTn sequences, is required for the induction of HSP70 expression by EM fields. Removal of the 900 base pair segment of the c-myc promoter eliminates the ability of EM fields to induce c-myc expression. Similarly, removal of the 70 bp region of the HSP70 promoter, with its three nCTCTn sequences, eliminates the response to EM fields. The nCTCTn sequences apparently act as electromagnetic field response elements (EMRE). To test if introducing EMREs imparts the ability to respond to applied EM fields, the 900 bp segment of the c-myc promoter (containing eight EMREs) was placed upstream of CAT or luciferase reporter constructs that were otherwise unresponsive to EM fields. EMREs-reporter constructs were transfected into HeLa cells and exposed to 8 microT 60 Hz fields. Protein extracts from EM field-exposed transfectants had significant increases in activity of both CAT and luciferase, compared with identical transfectants that were sham-exposed. Transfectants with CAT or luciferase constructs lacking EMREs remained unresponsive to EM fields, i.e., there was no increase in either CAT or luciferase activity. These data support the idea that EMREs can be used as switches to regulate exogenously introduced genes in gene therapy.

34. Litovitz TA, Kraus D, Penafiel M, Elson EC, Mullins JM. 1993. *The Role of Coherence Time in the Effect of Microwaves on Ornithine Decarboxylase Activity.* Bioelectromagnetics 14: 395-403. [http://www.ncbi.nlm.nih.gov/pubmed/8285913](http://www.ncbi.nlm.nih.gov/pubmed/8285913) **Abstract:** Previously, we demonstrated the requirements for a minimum coherence time of an applied, small amplitude (10 microT) ELF magnetic field if the field were to produce an enhancement of ornithine decarboxylase activity in L929 fibroblasts. Further investigation has revealed a remarkably similar coherence time phenomenon for enhancement of ornithine decarboxylase activity by amplitude-modulated 915 MHz microwaves of large amplitude (SAR 2.5 W/kg). Microwave fields modulated at 55, 60, or 65 Hz approximately doubled ornithine decarboxylase activity after 8 h. Switching modulation frequencies from 55 to 65 Hz at coherence times of 1.0 s or less abolished enhancement, while times of 10 s or longer provided full enhancement. Our **results** show that the microwave coherence effects are remarkably similar to those observed with ELF fields.

35. Lixia S, Yao K, Kajjun W, Deqiang L, Huajun H, Xiangwei G, Baohong W, Wei Z, Jianling L, Wei W. 2006. *Effects of 1.8GHz radiofrequency field on DNA damage and expression of heat shock protein 70 in human lens epithelial cells.* Mutat Res. 2006 Sep 29; [http://www.ncbi.nlm.nih.gov/pubmed/17011595](http://www.ncbi.nlm.nih.gov/pubmed/17011595) **Abstract:** To investigate the DNA damage, expression of heat shock protein 70 (Hsp70) and cell proliferation of human lens epithelial cells (hLEC) after exposure to the 1.8 GHz radiofrequency field (RF) of a global system for mobile communications (GSM). An Xc-1800 RF exposure system was used to employ a GSM signal at 1.8 GHz (217 Hz amplitude-modulated) with the output power in the specific absorption rate (SAR) of 1, 2 and 3 W/kg. After 2 h exposure to RF, the DNA damage of hLEC was accessed by comet assay at five different incubation times: 0, 30, 60, 120 and 240 min, respectively. Western blot and RT-PCR were used to determine the expression of Hsp70 in hLECs after RF exposure. The proliferation rate of cells was evaluated by bromodeoxyuridine incorporation on days 0, 1 and 4 after exposure. The results show that the difference of DNA-breaks between the exposed and sham-exposed (control) groups induced by 1
and 2 W/kg irradiation were not significant at any incubation time point (P > 0.05). The DNA damage caused by 3 W/kg irradiation was significantly increased at the times of 0 and 30 min after exposure (P < 0.05), a phenomenon that could not be seen at the time points of 60, 120 or 240 min (P > 0.05). Detectable mRNA as well as protein expression of Hsp70 was found in all groups. Exposure at SARs of 2 and 3 W/kg for 2 h exhibited significantly increased Hsp70 protein expression (P < 0.05), while no change in Hsp70 mRNA expression could be found in any of the groups (P > 0.05). No difference of the cell proliferation rate between the sham-exposed and exposed cells was found at any exposure dose tested (P > 0.05). The results indicate that exposure to non-thermal dosages of RF for wireless communications can induce no or repairable DNA damage and the increased Hsp70 protein expression in hLECs occurred without change in the cell proliferation rate. The non-thermal stress response of Hsp70 protein increase to RF exposure might be involved in protecting hLEC from DNA damage and maintaining the cellular capacity for proliferation.


Abstract: We demonstrate that reactive oxygen species (ROS) plays an important role in the process of apoptosis in human peripheral blood mononuclear cell (PBMC) which is induced by the radiation of 900 MHz radiofrequency electromagnetic field (RFEMF) at a specific absorption rate (SAR) of ~0.4 W/kg when the exposure lasts longer than two hours. The apoptosis is induced through the mitochondrial pathway and mediated by activating ROS and caspase-3, and decreasing the mitochondrial potential. The activation of ROS is triggered by the conformation disturbance of lipids, protein, and DNA induced by the exposure of GSM RFEMF. Although human PBMC was found to have a self-protection mechanism of releasing carotenoid in response to oxidative stress to lessen the further increase of ROS, the imbalance between the antioxidant defenses and ROS formation still results in an increase of cell death with the exposure time and can cause about 37% human PBMC death in eight hours.


Abstract: Radiofrequency fields of cellular phones may affect biological systems by increasing free radicals, which appear mainly to enhance lipid peroxidation, and by changing the antioxidase activities of human blood thus leading to oxidative stress. To test this, we have investigated the effect of acute exposure to radiofrequency fields of commercially available cellular phones on some parameters indicative of oxidative stress in 12 healthy adult male volunteers. Each volunteer put the phone in his pocket in standby position with the keypad facing the body. The parameters measured were lipid peroxide and the activities of superoxide dismutase (SOD), total glutathione peroxidase (GSH-Px) and catalase. The results obtained showed that the plasma level of lipid peroxide was significantly increased after 1, 2 and 4 h of exposure to radiofrequency fields of the cellular phone in standby position. Moreover, the activities of SOD and GSH-Px in human erythrocytes showed significant reduction while the activity of catalase in human erythrocytes did not decrease significantly. These results indicate that acute exposure to radiofrequency fields of commercially available cellular phones may modulate the oxidative stress of free radicals by enhancing lipid peroxidation and reducing the activation of SOD and GSH-Px, which are free radical scavengers. Therefore, these results support the interaction of radiofrequency fields of cellular phones with biological systems.


Abstract: This study was designed to demonstrate the
effects of 900-MHz electromagnetic field (EMF) emitted from cellular phone on brain tissue and also blood malondialdehyde (MDA), glutathione (GSH), retinol (vitamin A), vitamin D(3) and tocopherol (vitamin E) levels, and catalase (CAT) enzyme activity of guinea pigs. Fourteen male guinea pigs, weighing 500-800 g were randomly divided into one of two experimental groups: control and treatment (EMF-exposed), each containing seven animals. Animals in treatment group were exposed to 890- to 915-MHz EMF (217-Hz pulse rate, 2-W maximum peak power, SAR 0.95 w/kg) of a cellular phone for 12 h/day (11-h 45-min stand-by and 15-min spiking mode) for 30 days. Control guinea pigs were housed in a separate room without exposing EMF of a cellular phone. Blood samples were collected through a cardiac puncture and brains were removed after decapitation for the biochemical analysis at the end of the 30 days of experimental period. It was found that the MDA level increased (P<0.05), GSH level and CAT enzyme activity decreased (P<0.05), and vitamins A, E and D(3) levels did not change (P>0.05) in the brain tissues of EMF-exposed guinea pigs. In addition, MDA, vitamins A, D(3) and E levels, and CAT enzyme activity increased (P<0.05), and GSH level decreased (P<0.05) in the blood of EMF-exposed guinea pigs. It was concluded that electromagnetic field emitted from cellular phone might produce oxidative stress in brain tissue of guinea pigs. However, more studies are needed to demonstrate whether these effects are harmful or/and affect the neural functions.

39. Nylund R, Leszczynski D. 2004. Proteomics analysis of human endothelial cell line EA.hy926 after exposure to GSM 900 radiation. Proteomics 4:1359-1365. http://www.ncbi.nlm.nih.gov/pubmed/15188403 Abstract: The human endothelial cell line EA.hy926 was exposed to mobile phone radiation and the effect on protein expression was examined using two-dimensional electrophoresis (2-DE). Up to 38 various proteins have statistically significantly altered their expression levels following the irradiation. Four proteins were identified with matrix-assisted laser desorption/ionization-mass spectrometry (MALDI-MS). Two of the affected proteins were determined to be isoforms of cytoskeletal vimentin. This finding supports our earlier presented working hypothesis which indicated that the mobile phone radiation might affect the cytoskeleton and might have an effect on the physiological functions that are regulated by the cytoskeleton.

40. Nylund R, Leszczynski D. 2006. Mobile phone radiation causes changes in gene and protein expression in human endothelial cell lines and the response seems to be genome- and proteome-dependent. Proteomics. 2006 Jul 28; http://www.ncbi.nlm.nih.gov/pubmed/16878295 Abstract: We have examined in vitro cell response to mobile phone radiation (900 MHz GSM signal) using two variants of human endothelial cell line: EA.hy926 and EA.hy926v1. Gene expression changes were examined in three experiments using cDNA Expression Arrays and protein expression changes were examined in ten experiments using 2-DE and PDQuest software. Obtained results show that gene and protein expression were altered, in both examined cell lines, in response to one hour mobile phone radiation exposure at an average specific absorption rate of 2.8 W/kg. However, the same genes and proteins were differently affected by the exposure in each of the cell lines. This suggests that the cell response to mobile phone radiation might be genome- and proteome-dependent. Therefore, it is likely that different types of cells and from different species might respond differently to mobile phone radiation or might have different sensitivity to this weak stimulus. Our findings might also explain, at least in part, the origin of discrepancies in replication studies between different laboratories.

41. Oktem F, Ozguner F, Mollaoglu H, Koyu A, Uz E. 2005. Oxidative Damage in the Kidney Induced by 900-MHz-Emitted Mobile Phone: Protection by Melatonin. Arch Med Res.36:350-355. http://www.ncbi.nlm.nih.gov/pubmed/15950073 Abstract: BACKGROUND: The mobile phones emitting 900-MHz electromagnetic radiation (EMR) may be mainly absorbed by kidneys because they are often carried in belts. Melatonin, the chief secretory product of the pineal gland, was recently found to be a potent free radical scavenger and antioxidant. The aim of this study was to examine 900-MHz mobile phone-induced oxidative stress that promotes production of reactive oxygen species (ROS) on
renal tubular damage and the role of melatonin on kidney tissue against possible oxidative damage in rats. METHODS: The animals were randomly grouped as follows: 1) sham-operated control group and 2) study groups: i) 900-MHz EMR exposed (30 min/day for 10 days) group and ii) 900-MHz EMR exposed+melatonin (100 microg kg(-1) s.c. before the daily EMR exposure) treated group. Malondialdehyde (MDA), an index of lipid peroxidation, and urine N-acetyl-beta-d-glucosaminidase (NAG), a marker of renal tubular damage were used as markers of oxidative stress-induced renal impairment. Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) activities were studied to evaluate the changes of antioxidant status. RESULTS: In the EMR-exposed group, while tissue MDA and urine NAG levels increased, SOD, CAT, and GSH-Px activities were reduced. Melatonin treatment reversed these effects as well. In this study, the increase in MDA levels of renal tissue and in urine NAG and also the decrease in renal SOD, CAT, GSH-Px activities demonstrated the role of oxidative mechanism induced by 900-MHz mobile phone exposure, and melatonin, via its free radical scavenging and antioxidant properties, ameliorated oxidative tissue injury in rat kidney. CONCLUSIONS: These results show that melatonin may exhibit a protective effect on mobile phone-induced renal impairment in rats.

42. Ozguner F, Bardak Y, Comlekci S. Protective effects of melatonin and caffeic acid phenethyl ester against retinal oxidative stress in long-term use of mobile phone: a comparative study. Mol Cell Biochem. 2006 Jan;282(1-2):83-8. http://www.ncbi.nlm.nih.gov/pubmed/16317515 Abstract: There are numerous reports on the effects of electromagnetic radiation (EMR) in various cellular systems. Melatonin and caffeic acid phenethyl ester (CAPE), a component of honeybee propolis, were recently found to be potent free radical scavengers and antioxidants. Mechanisms of adverse effects of EMR indicate that reactive oxygen species may play a role in the biological effects of this radiation. The present study was carried out to compare the efficacy of the protective effects of melatonin and CAPE against retinal oxidative stress due to long-term exposure to 900 MHz EMR emitting mobile phones. Melatonin and CAPE were administered daily for 60 days to the rats prior to their EMR exposure during our study. Nitric oxide (NO, an oxidant product) levels and malondialdehyde (MDA, an index of lipid peroxidation), were used as markers of retinal oxidative stress in rats following to use of EMR. Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) activities were studied to evaluate the changes of antioxidant status in retinal tissue. Retinal levels of NO and MDA increased in EMR exposed rats while both melatonin and CAPE caused a significant reduction in the levels of NO and MDA. Likewise, retinal SOD, GSH-Px and CAT activities decreased in EMR exposed animals while melatonin and CAPE caused a significant increase in the activities of these antioxidant enzymes. Treatment of EMR exposed rats with melatonin or CAPE increased the activities of SOD, GSH-Px and CAT to higher levels than those of control rats. In conclusion, melatonin and CAPE reduce retinal oxidative stress after long-term exposure to 900 MHz emitting mobile phone. Nevertheless, there was no statistically significant difference between the efficacies of these two antioxidants against to EMR induced oxidative stress in rat retina. The difference was in only GSH-Px activity in rat retina. Melatonin stimulated the retinal GSH-Px activity more efficiently than CAPE did.

43. Ozguner F, Altinbas A, Ozaydin M, Dogan A, Vural H, Kisioglu AN, Cesur G, Yildirim NG. Mobile phone-induced myocardial oxidative stress: protection by a novel antioxidant agent caffeic acid phenethyl ester. Toxicol Ind Health. 2005 Oct;21(9):223-30. http://www.ncbi.nlm.nih.gov/pubmed/16132717 Abstract: Caffeic acid phenethyl ester (CAPE), a flavonoid like compound, is one of the major components of honeybee propolis. It has been used in folk medicine for many years in Middle East countries. It was found to be a potent free radical scavenger and antioxidant recently. The aim of this study was to examine long-term applied 900 MHz emitting mobile phone-induced oxidative stress that promotes production of reactive oxygen species (ROS) and, was to investigate the role of CAPE on kidney tissue against the possible electromagnetic radiation (EMR)-induced renal impairment in rats. In particular, the ROS such as superoxide and nitric oxide (NO) may
contribute to the pathophysiology of EMR-induced renal impairment. Malondialdehyde (MDA, an index of lipid peroxidation) levels, urinary N-acetyl-beta-D-glucosaminidase (NAG, a marker of renal tubular injury) and nitric oxide (NO, an oxidant product) levels were used as markers of oxidative stress-induced renal impairment and the success of CAPE treatment. The activities of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) in renal tissue were determined to evaluate the changes of antioxidant status. The rats used in the study were randomly grouped (10 each) as follows: i) Control group (without stress and EMR), ii) Sham-operated rats stayed without exposure to EMR (exposure device off), iii) Rats exposed to 900 MHz EMR (EMR group), and iv) A 900 MHz EMR exposed + CAPE treated group (EMR + CAPE group). In the EMR exposed group, while tissue MDA, NO levels and urinary NAG levels increased (p < 0.0001), the activities of SOD, CAT, and GSH-Px in renal tissue were reduced (p < 0.001). CAPE treatment reversed these effects as well (p < 0.0001, p < 0.001 respectively). In conclusion, the increase in NO and MDA levels of renal tissue, and in urinary NAG with the decrease in renal SOD, CAT, GSH-Px activities demonstrate the role of oxidative mechanisms in 900 MHz mobile phone-induced renal tissue damage, and CAPE, via its free radical scavenging and antioxidant properties, ameliorates oxidative renal damage. These results strongly suggest that CAPE exhibits a protective effect on mobile phone-induced and free radical mediated oxidative renal impairment in rats.

44. Ozguner F, Oktem F, Ayata A, et al. A novel antioxidant agent caffeic acid phenethyl ester prevents long-term mobile phone exposure-induced renal impairment in rat. Mol Cell Biochem 2005; 277: 73-80. http://www.ncbi.nlm.nih.gov/pubmed/16132717 Abstract: Caffeic acid phenethyl ester (CAPE), a flavonoid like compound, is one of the major components of honeybee propolis. It has been used in folk medicine for many years in Middle East countries. It was found to be a potent free radical scavenger and antioxidant recently. The aim of this study was to examine long-term applied 900 MHz emitting mobile phone-induced oxidative stress that promotes production of reactive oxygen species (ROS) and, was to investigate the role of CAPE on kidney tissue against the possible electromagnetic radiation (EMR)-induced renal impairment in rats. In particular, the ROS such as superoxide and nitric oxide (NO) may contribute to the pathophysiology of EMR-induced renal impairment. Malondialdehyde (MDA, an index of lipid peroxidation) levels, urinary N-acetyl-beta-D-glucosaminidase (NAG, a marker of renal tubular injury) and nitric oxide (NO, an oxidant product) levels were used as markers of oxidative stress-induced renal impairment and the success of CAPE treatment. The activities of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) in renal tissue were determined to evaluate the changes of antioxidant status. The rats used in the study were randomly grouped (10 each) as follows: i) Control group (without stress and EMR), ii) Sham-operated rats stayed without exposure to EMR (exposure device off), iii) Rats exposed to 900 MHz EMR (EMR group), and iv) A 900 MHz EMR exposed + CAPE treated group (EMR + CAPE group). In the EMR exposed group, while tissue MDA, NO levels and urinary NAG levels increased (p < 0.0001), the activities of SOD, CAT, and GSH-Px in renal tissue were reduced (p < 0.001). CAPE treatment reversed these effects as well (p < 0.0001, p < 0.001 respectively). In conclusion, the increase in NO and MDA levels of renal tissue, and in urinary NAG with the decrease in renal SOD, CAT, GSH-Px activities demonstrate the role of oxidative mechanisms in 900 MHz mobile phone-induced renal tissue damage, and CAPE, via its free radical scavenging and antioxidant properties, ameliorates oxidative renal damage. These results strongly suggest that CAPE exhibits a protective effect on mobile phone-induced and free radical mediated oxidative renal impairment in rats.

of 16 Hz and 60 Hz produced a transient increase in ODC activity that reached a peak at 8 h of exposure and returned to control levels after 24 h of exposure. In this case, ODC was increased by a maximum of 90% relative to control levels. A 40% increase in ODC activity was also observed after 8 h of exposure with a typical signal from a TDMA digital cellular telephone operating in the middle of its transmission frequency range (approximately 840 MHz). This signal was burst modulated at 50 Hz, with approximately 30% duty cycle. By contrast, 8 h exposure with 835 MHz microwaves amplitude modulated with speech produced no significant change in ODC activity. Further investigations, with 8 h of exposure to AM microwaves, as a function of modulation frequency, revealed that the response is frequency dependent, decreasing sharply at 6 Hz an 600 Hz. Exposure with 835 MHz microwaves, frequency modulated with a 60 Hz sinusoid, yielded no significant enhancement in ODC activity for exposure times ranging between 2 and 24 h. Similarly, exposure with a typical signal from an AMPS analog cellular telephone, which uses a form of frequency modulation, produced no significant enhancement in ODC activity. Exposure with 835 MHz continuous wave microwaves produced no effects for exposure times between 2 and 24 h, except for a small but statistically significant enhancement in ODC activity after 6 h of exposure. Comparison of these results suggests that effects are much more robust when the modulation causes low-frequency periodic changes in the amplitude of the microwave carrier.


http://www.ncbi.nlm.nih.gov/pubmed/12210755 Abstract: To determine if microwave exposure could elicit a biological effect in the absence of thermal stress, studies were designed in which chick embryos were exposed to athermal microwave radiation (915 MHz) to look for induction of Hsp70, a protein produced during times of cellular stress that aids in the protection of cellular components. Levels of Hsp70 were found to increase within 2 h, with maximum expression (approximately 30% higher than controls) typically occurring by 3 h from the start of exposure. Other embryos were exposed to microwave radiation prior to being subjected to hypoxic stress, and were found to have significantly higher survival (P < 0.05) following re-oxygenation than non-exposed controls. The results of these studies indicate that not only can athermal microwave exposures activate the stress protein response pathway; they can also enhance survivability following exposure to a subsequent, potentially lethal stress. From a public health standpoint, it is important that more studies be performed to determine if repeated exposures, a condition likely to be found in cell phone use, are still beneficial.

48. Shahin S, Singh VP, Shukla RK, Dhawan A, Gangwar RK, Singh SP, Chaturvedi CM. 2.45 GHz Microwave Irradiation-Induced Oxidative Stress Affects Implantation or Pregnancy in Mice. Mus musculus. Appl Biochem Biotechnol 2013; [Copy filed in Docket] Abstract: The present experiment was designed to study the 2.45 GHz low-level microwave (MW) irradiation-induced stress response and its effect on implantation or pregnancy in female mice…We observed that implantation sites were affected significantly in MW-irradiated mice as compared to control. Further, in addition to a significant increase in ROS, hemoglobin (p<0.01), RBC and WBC counts (p<0.01), N/L ratio (p<0.001), DNA damage (p<0.001) in brain cells, and plasma estradiol concentration (p<0.05), a significant decrease was observed in NO level (p<0.05) and antioxidant enzyme activities of MW-exposed mice. Our findings led us to conclude that a low level of MW irradiation-induced oxidative stress not only suppresses implantation, but it may also lead to deformity of the embryo in case pregnancy continues. We also suggest that MW radiation-induced oxidative stress by increasing ROS production in the body may lead
to DNA strand breakage in the brain cells and implantation failure/resorption or abnormal pregnancy in mice.

Abstract: PURPOSE: The aim of the study was to evaluate the intensity of oxidative stress in the brain of animals chronically exposed to mobile phones and potential protective effects of melatonin in reducing oxidative stress and brain injury.MATERIALS AND METHODS:Experiments were performed on Wistar rats exposed to microwave radiation during 20, 40 and 60 days. Four groups were formed: I group (control)- animals treated by saline, intraperitoneally (i.p.) applied daily during follow up, II group (Mel)- rats treated daily with melatonin (2 mg kg(-1) body weight i.p.), III group (MWs)- microwave exposed rats, IV group (MWs + Mel)-MWs exposed rats treated with melatonin (2 mg kg(-1) body weight i.p.). The microwave radiation was produced by a mobile test phone (SAR = 0.043-0.135 W/kg). RESULTS: A significant increase in the brain tissue malondialdehyde (MDA) and carbonyl group concentration was registered during exposure. Decreased activity of catalase (CAT) and increased activity of xanthine oxidase (XO) remained after 40 and 60 days of exposure to mobile phones. Melatonin treatment significantly prevented the increase in the MDA content and XO activity in the brain tissue after 40 days of exposure while it was unable to prevent the decrease of CAT activity and increase of carbonyl group contents. CONCLUSION: We demonstrated two important findings; that mobile phones caused oxidative damage biochemically by increasing the levels of MDA, carbonyl groups, XO activity and decreasing CAT activity; and that treatment with the melatonin significantly prevented oxidative damage in the brain.

Abstract: The aim of the paper was to estimate in vitro the effect of electromagnetic field produced by mobile phones on the activity of superoxide dismutase (SOD-1) in human blood platelets. Suspension of blood platelets exposed to the electromagnetic field of 900 MHz frequency for 1, 3, 5, 7 minutes. Our studies demonstrated that microwaves produced by mobiles significantly depleted the activity of SOD-1 after 1, 5, 7 min. of exposition and increased after 3 min. in comparison with control test. On the ground of our results we conclude that oxidative stress after exposition to microwaves can be the reason of many disadvantageous changes in cells and may cause many systemic consequences in human organism.

Abstract: Accumulating evidence suggests that exposure to radiofrequency electromagnetic field (RF-EMF) can have various biological effects. In this study the oxidative and genotoxic effects were investigated in earthworms Eisenia fetida exposed in vivo to RF-EMF at the mobile phone frequency (900MHz). Earthworms were exposed to the homogeneous RF-EMF at field levels of 10, 23, 41 and 120Vm(-1) for a period of 2h using a Gigahertz Transversal Electromagnetic (GTEM) cell. At the field level of 23Vm(-1) the effect of longer exposure (4h) and field modulation (80% AM 1kHz sinusoidal) was investigated as well. All exposure treatments induced significant genotoxic effect in earthworms coelomocytes detected by the Comet assay, demonstrating DNA damaging capacity of 900MHz electromagnetic radiation. Field modulation additionally increased the genotoxic effect. Moreover, our results indicated the induction of antioxidant stress response in terms of enhanced catalase and glutathione reductase activity as a result of the RF-EMF exposure, and demonstrated the generation of lipid and protein oxidative damage.
Antioxidant responses and the potential of RF-EMF to induce damage to lipids, proteins and DNA differed depending on the field level applied, modulation of the field and duration of E. fetida exposure to 900MHz electromagnetic radiation. Nature of detected DNA lesions and oxidative stress as the mechanism of action for the induction of DNA damage are discussed.

52. Tkalec M, Malaric K, Pevalek-Kozlina B. Exposure to radiofrequency radiation induces oxidative stress in duckweed Lemna minor L. Sc Tot Env 2007; 388: 78-89. http://www.ncbi.nlm.nih.gov/pubmed/17825879 Abstract: Widespread use of radiofrequency radiation emitting devices increased the exposure to electromagnetic fields (EMFs) from 300 MHz to 300 GHz. Various biological effects of exposure to these fields have been documented so far, but very little work has been carried out on plants. The aim of the present work was to investigate the physiological responses of the plant Lemna minor after exposure to radiofrequency EMFs, and in particular, to clarify the possible role of oxidative stress in the observed effects. Duckweed was exposed for 2 h to EMFs of 400 and 900 MHz at field strengths of 10, 23, 41 and 120 V m(-1). The effect of a longer exposure time (4 h) and modulation was also investigated. After exposure, parameters of oxidative stress, such as lipid peroxidation, H(2)O(2) content, activities and isoenzyme pattern of antioxidative enzymes as well as HSP70 expression were evaluated. At 400 MHz, lipid peroxidation and H(2)O(2) content were significantly enhanced in duckweed exposed to EMFs of 23 and 120 V m(-1) while other exposure treatments did not have an effect. Compared to the controls, the activities of antioxidative enzymes showed different behaviour: catalase (CAT) activity increased after most exposure treatments while pyrogallol (PPX) and ascorbate peroxidase (APX) activities were not changed. Exceptions were reduced PPX and APX activity after longer exposure at 23 V m(-1) and increased PPX activity after exposures at 10 and 120 V m(-1). By contrast, at 900 MHz almost all exposure treatments significantly increased level of lipid peroxidation and H(2)O(2) content but mostly decreased PPX activity and did not affect CAT activity. Exceptions were exposures to a modulated field and to the field of 120 V m(-1) which increased PPX and CAT activity. At this frequency APX activity was significantly decreased after exposure at 10 V m(-1) and longer exposure at 23 V m(-1) but it increased after a shorter exposure at 23 V m(-1). At both frequencies no differences in isoenzyme patterns of antioxidative enzymes or HSP70 level were found between control and exposed plants. Our results showed that non-thermal exposure to investigated radiofrequency fields induced oxidative stress in duckweed as well as unspecific stress responses, especially of antioxidative enzymes. However, the observed effects markedly depended on the field frequencies applied as well as on other exposure parameters (strength, modulation and exposure time). Enhanced lipid peroxidation and H(2)O(2) content accompanied by diminished antioxidative enzymes activity caused by exposure to investigated EMFs, especially at 900 MHz, indicate that oxidative stress could partly be due to changed activities of antioxidative enzymes.

53. Wang LF, Hu XJ, Peng RY, Wang SM, Gao YB, Dong J, Zhao L, Li X, Zuo HY, Wang CZ, Gao RL, Su ZT, Feng XX. Application of 1H-NMR-based metabolomics for detecting injury induced by long-term microwave exposure in Wistar rats' urine. Anal Bioanal Chem. 2012 Jul;404(1):69-78. http://www.ncbi.nlm.nih.gov/pubmed/22706401 Abstract: There has been growing public concern regarding exposure to microwave fields as a potential human health hazard. This study aimed to identify sensitive biochemical indexes for the detection of injury induced by microwave exposure. Male Wistar rats were exposed to microwaves for 6 min per day, 5 days per week over a period of 1 month at an average power density of 5 mW/cm(2) (specific absorption rate of 2.1 W/kg). Urine specimens were collected over 24 h in metabolic cages at 7 days, 21 days, 2 months, and 6 months after exposure. (1)H NMR spectroscopy data were analyzed using multivariate statistical techniques. Urine metabolic profiles of rats after long-term microwave exposure were significantly differentiated from those of sham-treated controls using principal component analysis or partial least squares discriminant analysis. Significant differences in low molecular weight metabolites (acetate, succinate, citrate, ketoglutarate, glucose, taurine, phenylalanine, tyrosine, and hippurate) were identified in the 5 mW/cm(2) microwave exposure...
group compared with the sham-treated controls at 7 days, 21 days, and 2 months. Metabolites returned to normal levels by 6 months after exposure. These data indicated that these metabolites were related to the perturbations of energy metabolism particularly in the tricarboxylic acid cycle, and the metabolism of amino acids, monoamines, and choline in urine represent potential indexes for the detection of injury induced by long-term microwave exposure.

54. *Xu S, Zhou Z, Zhang L, et al. Exposure to 1800MHz radiofrequency radiation induces oxidative damage to mitochondrial DNA in primary cultured neurons. Brain Research. 2010;1311:189–196. [PubMed] Abstract: Increasing evidence indicates that oxidative stress may be involved in the adverse effects of radiofrequency (RF) radiation on the brain. Because mitochondrial DNA (mtDNA) defects are closely associated with various nervous system diseases and mtDNA is particularly susceptible to oxidative stress, the purpose of this study was to determine whether radiofrequency radiation can cause oxidative damage to mtDNA. In this study, we exposed primary cultured cortical neurons to pulsed RF electromagnetic fields at a frequency of 1800 MHz modulated by 217 Hz at an average special absorption rate (SAR) of 2 W/kg. At 24 h after exposure, we found that RF radiation induced a significant increase in the levels of 8-hydroxyguanine (8-OHdG), a common biomarker of DNA oxidative damage, in the mitochondria of neurons. Concomitant with this finding, the copy number of mtDNA and the levels of mitochondrial RNA (mtRNA) transcripts showed an obvious reduction after RF exposure. Each of these mtDNA disturbances could be reversed by pretreatment with melatonin, which is known to be an efficient antioxidant in the brain. Together, these results suggested that 1800 MHz RF radiation could cause oxidative damage to mtDNA in primary cultured neurons. Oxidative damage to mtDNA may account for the neurotoxicity of RF radiation in the brain.

55. Yurekli AI, Ozkan M, Kalkan T, Saybasili H, Tuncel H, Atukeren P, Gumustas K, Seker S. GSM base station electromagnetic radiation and oxidative stress in rats. Electromagn Biol Med. 2006;25(3):177-88. http://www.ncbi.nlm.nih.gov/pubmed/16954120 Abstract: The ever increasing use of cellular phones and the increasing number of associated base stations are becoming a widespread source of nonionizing electromagnetic radiation. Some biological effects are likely to occur even at low-level EM fields. In this study, a gigahertz transverse electromagnetic (GTEM) cell was used as an exposure environment for plane wave conditions of far-field free space EM field propagation at the GSM base transceiver station (BTS) frequency of 945 MHz, and effects on oxidative stress in rats were investigated. When EM fields at a power density of 3.67 W/m2 (specific absorption rate = 11.3 mW/kg), which is well below current exposure limits, were applied, MDA (malondialdehyde) level was found to increase and GSH (reduced glutathione) concentration was found to decrease significantly (p < 0.0001). Additionally, there was a less significant (p = 0.0190) increase in SOD (superoxide dismutase) activity under EM exposure.

13.B Studies describing the role of oxidative stress in DNA damage, cancer, neurodegenerative diseases and human fertility:

influence the development of reproductive disorders such as endometriosis and preeclampsia. Although the pathogenesis of preeclampsia has yet to be determined, placental ischemia/hypoxia is regarded as an important contributor through the induction of OS, which in turn can trigger the endothelial cell dysfunction characteristic of the disease.

57. Cooke MS, Evans MD, Dizdaroglu M, Lunec J. Oxidative DNA damage: mechanisms, mutation, and disease. FASEB J. 2003 Jul;17(10):1195-214. Review. http://www.fasebj.org/content/17/10/1195.long Abstract: Oxidative DNA damage is an inevitable consequence of cellular metabolism, with a propensity for increased levels following toxic insult. Although more than 20 base lesions have been identified, only a fraction of these have received appreciable study, most notably 8-oxo-2'deoxyguanosine. This lesion has been the focus of intense research interest and been ascribed much importance, largely to the detriment of other lesions. The present work reviews the basis for the biological significance of oxidative DNA damage, drawing attention to the multiplicity of proteins with repair activities along with a number of poorly considered effects of damage. Given the plethora of (often contradictory) reports describing pathological conditions in which levels of oxidative DNA damage have been measured, this review critically addresses the extent to which the in vitro significance of such damage has relevance for the pathogenesis of disease. It is suggested that some shortcomings associated with biomarkers, along with gaps in our knowledge, may be responsible for the failure to produce consistent and definitive results when applied to understanding the role of DNA damage in disease, highlighting the need for further studies.

58. Dizdaroglu M. Oxidatively induced DNA damage: mechanisms, repair and disease. Cancer Lett. 2012 Dec 31;327(1-2):26-47. Review. http://www.ncbi.nlm.nih.gov/pubmed/22293091 Abstract: Endogenous and exogenous sources cause oxidatively induced DNA damage in living organisms by a variety of mechanisms. The resulting DNA lesions are mutagenic and, unless repaired, lead to a variety of mutations and consequently to genetic instability, which is a hallmark of cancer. Oxidatively induced DNA damage is repaired in living cells by different pathways that involve a large number of proteins. Unrepaired and accumulated DNA lesions may lead to disease processes including carcinogenesis. Mutations also occur in DNA repair genes, destabilizing the DNA repair system. A majority of cancer cell lines have somatic mutations in their DNA repair genes. In addition, polymorphisms in these genes constitute a risk factor for cancer. In general, defects in DNA repair are associated with cancer. Numerous DNA repair enzymes exist that possess different, but sometimes overlapping substrate specificities for removal of oxidatively induced DNA lesions. In addition to the role of DNA repair in carcinogenesis, recent evidence suggests that some types of tumors possess increased DNA repair capacity that may lead to therapy resistance. DNA repair pathways are drug targets to develop DNA repair inhibitors to increase the efficacy of cancer therapy. Oxidatively induced DNA lesions and DNA repair proteins may serve as potential biomarkers for early detection, cancer risk assessment, prognosis and for monitoring therapy. Taken together, a large body of accumulated evidence suggests that oxidatively induced DNA damage and its repair are important factors in the development of human cancers. Thus this field deserves more research to contribute to the development of cancer biomarkers, DNA repair inhibitors and treatment approaches to better understand and fight cancer.

59. Frustaci A, Neri M, Cesario A, Adams JB, Domenici E, Bernardina BD, Bonassi S. 2012. Oxidative stress-related biomarkers in autism: Systematic review and meta-analyses. Free Radic Biol Med 52 (10):2128-41. Review http://www.ncbi.nlm.nih.gov/pubmed/22542447 Abstract: Autism spectrum disorders (ASDs) are rarely diagnosed in children younger than 2 years, because diagnosis is based entirely on behavioral tests. Oxidative damage may play a central role in this pathogenesis, together with the interconnected transmethylation cycle and transsulfuration pathway. In an attempt to clarify and quantify the relationship between oxidative stress-related blood biomarkers and ASDs, a systematic literature review was carried out. For each identified study, mean biomarker levels were compared in
cases and controls providing a point estimate, the mean ratio, for each biomarker. After meta-analysis, the ASD patients showed decreased blood levels of reduced glutathione (27%), glutathione peroxidase (18%), methionine (13%), and cysteine (14%) and increased concentrations of oxidized glutathione (45%) relative to controls, whereas superoxide dismutase, homocysteine, and cystathionine showed no association with ASDs. For the C677T allele in the methylene tetrahydrofolate reductase gene (MTHFR), homozygous mutant subjects (TT) showed a meta-OR of 2.26 (95% CI 1.30-3.91) of being affected by ASD with respect to the homozygous nonmutant (CC). Case-control studies on blood levels of vitamins suggest a lack of association (folic acid and vitamin B12) or rare association (vitamins A, B6, C, D, E). Sparse results were available for other biomarkers (ceruloplasmin, catalase, cysteinylglycine, thiobarbituric acid-reactive substances, nitric oxide) and for polymorphisms in other genes. Existing evidence is heterogeneous and many studies are limited by small sample size and effects. In conclusion, existing evidence suggests a role for glutathione metabolism, the transmethylation cycle, and the transsulfuration pathway, although these findings should be interpreted with caution, and larger, more standardized studies are warranted.

60. Kultz D. Molecular and Evolutionary Basis of the Cellular Stress Response. Ann Rev Physiol 2005. 67: 225-257. http://www.ncbi.nlm.nih.gov/pubmed/15709958  Abstract: The cellular stress response is a universal mechanism of extraordinary physiological/pathophysiological significance. It represents a defense reaction of cells to damage that environmental forces inflict on macromolecules. Many aspects of the cellular stress response are not stressor specific because cells monitor stress based on macromolecular damage without regard to the type of stress that causes such damage. Cellular mechanisms activated by DNA damage and protein damage are interconnected and share common elements. Other cellular responses directed at re-establishing homeostasis are stressor specific and often activated in parallel to the cellular stress response. All organisms have stress proteins, and universally conserved stress proteins can be regarded as the minimal stress proteome. Functional analysis of the minimal stress proteome yields information about key aspects of the cellular stress response, including physiological mechanisms of sensing membrane lipid, protein, and DNA damage; redox sensing and regulation; cell cycle control; macromolecular stabilization/repair; and control of energy metabolism. In addition, cells can quantify stress and activate a death program (apoptosis) when tolerance limits are exceeded.

61. Rao AV, Balachandran B. Role of oxidative stress and antioxidants in neurodegenerative diseases. Nutr Neurosci. 2002 Oct;5(5):291-309. http://www.ncbi.nlm.nih.gov/pubmed/12385592  Abstract: Neurodegenerative diseases (NDD) are a group of illness with diverse clinical importance and etiologies. NDD include motor neuron disease such as amyotrophic lateral sclerosis (ALS), cerebellar disorders, Parkinson's disease (PD), Huntington's disease (HD), cortical destructive Alzheimer's disease (AD) and Schizophrenia. The pathobiology of neurodegenerative disorders with emphasis on genetic origin and its correlation with oxidative stress of neurodegenerative disorders will be reviewed and the reasons as to why brain constitutes a vulnerable site of oxidative damage will be discussed. The article will also discuss the potential free radical scavenger, mechanism of antioxidant action of lycopene and the need for the use of antioxidants in the prevention of NDD