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Neurological Effects of
Radiofrequency Electromagnetic Radiation
Relating to Wireless Communication Technology

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Introduction

There is a general concern on the possible hazardous health effects of exposure to radiofrequency electromagnetic radiation (RFR) emitted from wireless communication devices. The following is a brief summary of scientific research on the effects of RFR exposure on the nervous system. For readers who are not familiar with the jargon of biological experiments, I have underlined the main conclusions of the research described.

Unlike the conditions in most previous research on the biological effects of RFR in which whole body exposure was studied, the effects of cellular telephone-related exposure involve repeated exposure with variable durations of a relatively constant amount of body tissue (i.e., part of the head). In considering the biological effects of RFR, the intensity and frequency of the radiation and exposure duration are important determinants of the responses. For repeated exposure, as in the case of the use of cellular telephones, homeostatic compensatory response can occur. On the other hand, since a relatively constant amount of body tissue is exposed, cumulative effect could occur and lead to an eventual breakdown of homeostasis and adverse health consequences. Data from some of the experiments described below do suggest that RFR effects are cumulative over time. Most of the energy from a cellular telephone antenna is deposited in the skin and the outer portion of the brain (cerebral cortex). From theoretical calculations (e.g., references 1-3), peak SAR in head tissue can range from 2-8 W/kg per watt output of the device. A logical concern is whether the deposited energy could locally affect the blood-brain-barrier. A transient change in blood-brain-barrier permeability could have important health consequences. In addition, possible morphological, metabolic, physiological, and genetic changes in neural tissues should also be considered. These effects could lead to temporary or permanent functional changes in the nervous system.

Blood-Brain-Barrier

The blood-brain-barrier is a biological barrier surrounding the brain. It blocks the entry of certain, and possibly harmful, molecules in the general blood circulation from entering the central nervous system. Studies on the effects of RFR on the blood-brain-barrier were performed on animals in vivo, and SARs, if reported, are mostly given as average whole body SAR. Local SARs at the surface of the brain, where the blood-brain-barrier is located, were usually not known. This limits the extrapolation of data in the existing literature to cellular telephone exposure.

With regard to the intensity of exposure, the conclusion from most of the studies is that a high intensity of RFR is required to alter the permeability of the blood-brain-barrier. Significant changes in brain or body temperature seem to be a necessary condition for the effect to occur. For example, Chang et al. [4] studied in the dog the penetration of ^{131}I-labeled albumin into the brain. The head of the dog was irradiated with 1000-MHz continuous-wave RFR at 2, 4, 10, 30, 50, or 200 mW/cm^2. At 30 mW/cm^2, 4 of the 11 dogs studied showed a significant increase in albumin penetration compared to that of sham-exposed animals, whereas no significant difference was seen at the other power densities. Lin and Lin [5] reported no significant change in the permeability of sodium fluorescein and Evan's blue into the brain of rats with focal exposure at the head for 20 min to pulsed 2450-MHz RFR at 0.5-1000 mW/cm^2 (local SARs 0.04-80 W/kg), but an increase was reported [6] after similar exposure of the head at an SAR of 240 W/kg, which increased the brain temperature to 43 ºC. In another study, Goldman et al. [7] used ^{86}Rb as a tracer to study the permeability of the blood-brain-barrier in the rat after 5, 10, or 20 min of exposure to 2450-MHz pulsed RFR at an average power density of 3 W/cm^2 (SAR 240 W/kg) on the left side of the head. Brain temperature of the animals was increased to 43 ºC by the radiation. Increases in ^{86}Rb uptake in various regions in the left hemisphere of the brain were observed. That increase in brain temperature played a critical role in the effect of RFR on the permeability of the blood-brain-barrier was further supported in an experiment by Neilly and Lin [8], in which they found that ethanol infusion could attenuate RFR-induced increase in penetration of Even's blue into the rat brain. Ethanol reduced RFR-induced increase in brain temperature. Sutton and Carroll [9] reported an increase in permeability of horseradish peroxidase into the brain of the rat, when the brain temperature was raised to 40-45 ºC by focal heating of the head with continuous-wave 2450-MHz RFR. In addition, cooling the body of the animals before exposure could counteract this effect of RFR. The conclusion that RFR-induced hyperthermia is a cause of the change in blood-brain-barrier permeability was further substantiated by a study by Moriyama et al. [10].

When low-intensity RFR was studied, generally, no significant effect on the blood-brain-barrier was observed. For example, Gruenau et al. [11] reported no significant change on the penetration of ^{14}C-sucrose into the brain of rats after 30 min of exposure to pulsed or continuous-wave 2800-MHz RFR of various intensities (1-15 mW/cm^2 for the pulsed radiation, 10 and 40 mW/cm^2 for the continuous-wave radiation). Ward et al. [12] irradiated rats with 2450-MHz RFR for 30 min at different power densities (0-30 mW/cm^2, SAR 0-6 W/kg) and studied entry of ^{3}H-inulin and ^{14}C-sucrose into different areas of the brain. They also reported no significant increase in penetration

of both compounds into the brain due to RFR exposure; but they reported an increase in ^{14}C-sucrose entry into the hypothalamus when the ambient temperature of exposure was at 40 $^{\circ}$C. This increase in permeability was suggested to be due to the hyperthermia induced in the animals exposed in high ambient temperature. In a further study, Ward and Ali [13] exposed rats to 1700-MHz continuous-wave or pulsed RFR for 30 min with the radiation concentrated at the head of the animal (SAR 0.1 W/kg). They reported no significant change in permeability into the brain of ^{3}H-inulin and ^{14}C-sucrose after the exposure. Williams et al. [14-17] carried out a series of experiments to study the effect of RFR exposure on blood-brain-barrier permeability to hydrophilic molecules in unrestrained, conscious rats. The effects of exposure to continuous-wave 2450-MHz RFR at 20 or 65 mW/cm^2 (SAR 4 or 13 W/kg) for 30, 90, or 180 min were compared with those of ambient heating (42 $^{\circ}$C)-induced hyperthermia and urea infusion, on sodium fluorescein, horseradish peroxidase, and ^{14}C-sucrose permeability into different areas of the brain. They concluded that RFR did not significantly affect the penetration of the tracers into the brain .

Even though most studies indicate that changes in brain-brain-barrier occurs only after exposure to RFR of high intensities with significant increase in tissue temperature, several studies have reported increases in permeability after exposure to RFR of relatively low intensities. Frey et al. [18] reported an increase in fluorescein in brain slices of rats injected with the dye and exposed for 30 min to continuous-wave 1200-MHz RFR (2.4 mW/cm^2, SAR 1.0 W/kg) as compared with control animals. Interestingly, a more pronounced effect was observed when the animals were exposed to pulsed 1200-MHz RFR at a lower average power density of 0.2 mW/cm^2. Pulsed RFR seemed to be more potent than continuous-wave RFR. However, these findings were not observed in a similar experiment by Merritt et al. [19].

An increase in the concentration of horseradish peroxidase was found in the brain of the Chinese hamster after 2 hr of irradiation to continuous-wave 2450-MHz RFR at 10 mW/cm^2 (SAR 2.5 W/kg) [20]. Increases in horseradish peroxidase permeability were also observed in the brains of rats and Chinese hamsters exposed for 2 hr to continuous-wave 2800-MHz RFR at 10 mW/cm^2 (SAR 0.9 W/kg for the rat and 1.9 W/kg for the Chinese hamster). Oscar and Hawkins [21] reported increased permeability of radioactive mannitol and inulin, and no significant change in dextrin permeability into the brain of rats exposed for 20 min to continuous-wave or pulsed 1300-MHz RFR at a power density of 1 mW/cm^2 (SAR 0.4 W/kg). Again, the effect of the pulsed radiation was more prominent. Preston et al. [22] suggested that an increase in regional blood flow in the brain could explain the results of Oscar and Hawkins [21]. Oscar et al. [23] did

observe an increased blood flow in various regions of the rat brain after 5 to 60 min of exposure to pulsed 2800-MHz (2 μs pulses, 500 pps) RFR at 1 or 15 mW/cm² (SARs 0.2 and 3 W/kg). In addition, Neubauer et al. [24] studied the penetration of rhodamine-ferritin complex into the blood-brain-barrier of the rat. The compound was administered to the animals and then they were irradiated with pulsed 2450-MHz RFR for 15, 30, 60, or 120 min at an average power density of 5 or 10 mW/cm² (SAR 2 W/kg). Capillary endothelial cells from the cerebral cortex of the rats were isolated immediately after exposure. An approximately two fold increase in the complex was found in cells of animals after 30 min or longer of exposure to the 10 mW/cm² radiation. No significant effect was observed at 5 mW/cm². Furthermore, pretreating the animals before exposure with the microtubular function inhibitor colchicine blocked the effect of the RFR. These data suggest an RFR-induced increase in pinocytotic activity in the cells forming the blood-brain-barrier. Recently, a series of experiments carried out by Salford and his associates [25] has shown an increase in permeability of albumin into the brain of rats exposed (2 hr) to continuous-wave and pulse-modulated (8, 16, 50, and 200 Hz) 915-MHz RFR (SAR 0.016-5 W/kg).

Thus, it is possible that exposure to RFR from cellular telephones can cause a transient localized change in blood flow, pinocytosis, or permeability of the blood-brain-barrier. These effects could lead to local changes in brain functions.

Cellular Morphology of the Brain

Radiofrequency radiation-induced morphological changes of the central nervous system are shown only to occur under relatively high intensity or prolonged exposure to the radiation [26-28]. However, there are several studies showing that *repeated* exposure at relatively low SARs caused morphological changes in the central nervous system. Gordon [27] and Tolgskaya and Gordon [28] reported changes in neuronal morphology in the rat brain after repeated exposure to RFR (3000 MHz, thirty five 30-min sessions, <10 mW/cm², SAR 2 W/kg). Baranski [29] reported edema and heat lesions in the brain of guinea pigs exposed in a single 3-hr session to 3000-MHz RFR at a power density of 25 mW/cm² (SAR 3.75 W/kg). After repeated exposure (3 hr/day for 30 days) to the radiation, myelin degeneration and glial cell proliferation were reported in the brains of exposed guinea pigs (3.5 mW/cm², SAR 0.53 W/kg) and rabbits (5 mW/cm², SAR 0.75 W/kg). Interestingly, pulsed (400 pps) RFR produced more pronounced effects in the nervous system of the guinea pig than continuous-wave radiation of the same power density. Switzer and Mitchell [30] also reported an increase in myelin figures

(degeneration) of neurons in the brain of rats at 6 weeks after repeated (5 hr/day, 5 day/week for 22 weeks) exposure to continuous-wave 2450-MHz RFR (SAR 2.3 W/kg). Another important area of research on morphological effects of RFR exposure, that could have important implication on cellular telephone use, is that on the eye. Damages to corneal endothelials, degenerative changes in cells of the iris and retina, and altered visual functions were reported in nonhuman primates after repeated exposure to RFR. Alarmingly, concomitant treatment with certain drugs can significantly sensitize these ocular responses to RFR. Effects were observed at an SAR of 0.26 W/kg [31,32].

Changes in morphology, especially cell death, could have an important implication on health. Injury-induced cell proliferation has been hypothesized as a cause of cancer [33].

Neural Electrophysiology

Exposure of neural tissue to RFR can conceivably cause electrophysiological changes in the nervous system. Changes in neuronal electrophysiology, evoked potentials, and EEG have been reported. Again, the possible involvement of of RFR-induced tissue heating cannot be ruled out in some of the experiments. However, some effects were observed at low intensities and after repeated exposure suggesting cumulative effect. Chou and Guy [34] exposed temperature-controlled samples of isolated frog sciatic nerves, cat saphenous nerve, and rabbit vagus nerve to 2450-MHz RFR. They reported no significant change in the characteristics of the compound action potentials in their samples during exposure to either continuous-wave (SARs 0.3-1500 W/kg) or pulsed (peak SARs 0.3-220 W/kg) radiation. Thus, no direct field stimulation of neural activity was observed. Arber and Lin [35] recorded from Helix aspersa neurons irradiated with continuous-wave 2450-MHz RFR (60 min at 12.9 W/kg) at different ambient temperatures. The irradiation induced a decrease in spontaneous firing at medium temperatures of 8 and 21 °C, but not at 28 °C. Interestingly, when the neurons were irradiated with noise-amplitude-modulated 2450-MHz RFR (20% AM, 2 Hz-20 kHz) at SARs of 6.8 and 14.4 W/kg, increased membrane resistance and spontaneous activity were observed. An interesting study has shown a direct effect of RFR on ion channels in cells. D'Inzeo et al. [36] showed a direct action of RFR on acetylcholine-related ion channels in cultured chick embryo myotube cells, using the patch-clamp technique. The cell culture was exposed to continuous-wave 10750-MHz RFR with the power density at the cell surface estimated to be a few $\mu W/cm^2$. (Power density of the incident field at the surface of the culture medium was 50 $\mu W/cm^2$.) Exposure to RFR

decreased the opening of acetylcholine channels and increased the rate of desensitization of acetylcholine receptors.

Several studies investigated the effects of RFR on evoked potentials in the brain. Johnson and Guy [37] recorded evoked potentials in the thalamus of cats in response to stimulation of the contralateral forepaw during exposure to continuous-wave 918-MHz RFR for 15 min at power densities of 1-40 mW/cm^2 at the head. A power density-dependent decrease in latency of some of the late component responses of the thalamic evoked potential was observed. These data were interpreted as that RFR affected the multisynaptic neural pathway, which relates neural information from the skin to the thalamus. Interestingly, warming the body of the animals decreased the latency of both the initial and late components of the evoked potential. Taylor and Ashleman [38] recorded spinal cord ventral root responses to electrical stimulation of the ipsilateral gastrocnemius nerve in cats. The spinal cord was irradiated with continuous-wave 2450-MHz RFR at an incident power of 7.5 W. Decreases in latency and amplitude of the reflex response were observed during exposure (3 min) and responses returned to normal immediately after exposure. They also reported that raising the temperature of the spinal cord produced electrophysiological effects similar to those of RFR.

Various studies investigated the effects of RFR exposure on EEG of animals. Baranski and Edelwejn [39] reported that acute pulsed RFR (20 mW/cm^2) had little effect on the EEG pattern of rabbits that were given phenobarbital; however, after chronic exposure (7 mW/cm^2, 200 hr), desynchronization was seen in the EEG after phenobarbital administration, whereas synchronization was observed in the controls. Goldstein and Sisko [40] also reported periods of alternating EEG desynchronization and synchronization in rabbits anesthetized with pentobarbital and then subjected to 5 min of continuous-wave 9300-MHz RFR (0.7-2.8 mW/cm^2). Duration of desynchronization correlated with the power density of the irradiation. Servantie et al. [41] reported that rats exposed for 10 days to 3000-MHz pulsed (1 μs pulses, 500-600 pps) RFR at 5 mW/cm^2 produced an EEG frequency in the occipital cortex (as revealed by spectral analysis) synchronous to the pulse frequency of the radiation. The effect persisted a few hours after the termination of exposure. The authors proposed that the pulsed RFR synchronized the firing pattern of cortical neurons. Bawin et al. [42] exposed cats to 147-MHz RFR amplitude-modulated at 8 and 16 Hz at 1 mW/cm^2. They reported changes in both spontaneous and conditioned EEG patterns. Interestingly, the effects were not observed at lower or higher frequencies of modulation, suggesting a frequency window effect. Chizhenkova [43] recorded in the unanesthetized rabbits slow wave EEG in the motor and visual cortex, evoked potential in the visual cortex to light flashes, and single

unit activity in the visual cortex during and after exposure to continuous-wave RFR (wavelength = 12.5 cm, 40 mW/cm^2, 1 min exposure to the head). She reported a decrease in the threshold of visual evoked potential and an increase in excitability of visual cortical cells as a result of RFR exposure.

Several studies reported changes in EEG after prolonged repeated exposure to RFR. In some of these studies, RFR of relatively low power densities was used. Dumansky and Shandala [44] reported in the rat and rabbit that changes in EEG rhythm occurred after chronic RFR exposure (120 days, 8 hr/day) using a range of power densities. The researchers interpreted their results as an initial increase in excitability of the brain after RFR exposure followed by inhibition (cortical synchronization and slow wave) after prolonged exposure. Shandala et al. [45] exposed rabbits to 2375-MHz RFR (0.01-0.5 mW/cm^2) 7 h/day for 3 months. A pitfall of this study is that metallic electrodes were implanted in various regions of the brain (both subcortical and cortical areas) for electrical recording during the exposure period and post exposure. Metallic electrodes can interfere with the RFR fields. After 1 month of exposure at 0.1 mW/cm^2, they observed in the sensory/motor and visual cortex an increase in alpha rhythm, an EEG pattern indicative of relaxed and resting states of an animal. An increase in activity in the thalamus and hypothalamus was also observed later. Similar effects were also seen in animals exposed to the RFR at 0.05 mW/cm^2; however, rats exposed to a power density of 0.5 mW/cm^2 showed an increase in delta waves of high amplitude in the cerebral cortex after 2 weeks of exposure, suggesting a suppressive effect on EEG activity.

Takashima et al. [46] also studied the EEG patterns in rabbits exposed to RFR fields (1-30 MHz) amplitude-modulated at either 15 or 60 Hz. Acute exposure (2-3 hr, field strength 60-500 V$_{rms}$/m) elicited no observable effect. Chronic exposure (2 hr/day for 4-6 weeks at 90-500 V$_{rms}$/m) produced abnormal patterns including high amplitude spindles, bursts, and suppression of normal activity (shift to pattern of lower frequencies) when recorded within a few hours after exposure. In a chronic exposure experiment, Chou et al. [47] exposed rabbits to continuous-wave 2450-MHz RFR at 1.5 mW/cm^2 (2 hr/day, 5 days/week for 90 days). Electroencephalograph and evoked potentials were measured at the sensory-motor and occipital cortex at various times during the exposure period. The researchers reported large variations in the data and a tendency toward a decreased response amplitude in the latter part of the experiment, i.e., after a longer period of repeated exposure.

Changes in Neurotransmitter Functions

 Neurotransmitters are molecules that transmit information from one nerve cell to another. There are different types of neurotransmitter in the brain. Early studies have reported changes in various neurotransmitters (catecholamines, serotonin, and acetylcholine) in the brain of animals only after exposure to high intensities of RFR [48-51]. However, there are more recent studies that show changes in neurotransmitter functions after exposure to low intensities of RFR. Furthermore, studies indicate a dynamic response of the nervous system to RFR depending on the duration and number of exposure, and interaction of these two parameters. In addition, different brain regions could respond differently to RFR.

 In one study [52], rats were exposed to 2375-MHz RFR at power densities of 50 and 500 μW/cm^2 for 30 days (7 hr/day). At 50 μW/cm^2, brain epinephrine was increased on the 20th day of exposure, but returned to normal by day 30. There were slight increases in norepinephrine and dopamine concentrations throughout the exposure period. At 500 μW/cm^2, concentrations of all three neurotransmitters were increased on day 5, but declined continually after further exposure. In another study [29], acute exposure to pulsed RFR (~3000 MHz) at 25 mW/cm^2 was shown to cause a decrease in acetylcholine esterase (AChE) activity in the guinea pig brain. After three months (3 hr/day) of exposure at a power density of 3.5 mW/cm^2, an increase in brain AChE was observed. Dutta et al. [53] also reported an increase in AChE activity in neuroblastoma cells in culture after 30 min of exposure to 147-MHz RFR amplitude-modulated at 16 Hz at SARs of 0.05 and 0.02 W/kg, but not at 0.005, 0.01, or 0.1 W/kg, indicating a power window effect.

 Lai et al. [54,55] performed experiments to investigate the effects of RFR exposure on the cholinergic systems in the brain of the rat. Activity of the two main cholinergic pathways, septo-hippocampal and basalis-cortical pathways, was monitored by measuring sodium-dependent high-affinity choline uptake (HACU) from brain tissues. We found that after 45 min of acute exposure to pulsed 2450-MHz RFR (2 μs pulses, 500 pps, 1 mW/cm^2, average whole body SAR 0.6 W/kg), HACU was decreased in the hippocampus and frontal cortex, whereas no significant effect was observed in the striatum, hypothalamus, and inferior colliculus [56]. Interestingly, the effect of RFR on HACU in the hippocampus was blocked by pretreating the rats with the opiate-antagonists naloxone and naltrexone, suggesting that RFR activates endogenous opioids in the brain. Endogenous opioids are neurotransmitters with morphine-like properties and involved in many important physiological and behavioral functions, such as pain perception and motivation.

When different power densities of RFR were used, a dose-response relationship could be established from each brain region [57]. Data were analyzed by probit analysis, which enables a statistical comparison of the dose-response functions of the different brain regions. It was found that a higher dose-rate was needed to elicit a change in HACU in the striatum, whereas the responses of the frontal cortex and hippocampus were similar. Thus, under the same irradiation conditions, different brain regions could have different sensitivities to RFR.

In experiments to investigate the contributory effect of different parameters of RFR exposure, we found that the radiation caused a duration-dependent biphasic effect on cholinergic activity in the brain [56]. After 20 instead of 45 min of RFR exposure as in earlier experiments, an increase in HACU was observed in the frontal cortex, hippocampus, and hypothalamus of the rat . Thus, our data suggest that the response to RFR depends on the brain area studied and also on the duration of exposure.

Changes in transmitter receptors have also been reported in animals after exposure to RFR. These changes would indicate a more long term effect of RFR. After ten daily sessions of RFR exposure (2450 MHz at an average whole body SAR of 0.6 W/kg), the concentration of muscarinic cholinergic receptors changed in the brain [56, 58]. However, the direction of change depended on the acute effect of the RFR. When animals were given daily sessions of 20-min exposure, which increased cholinergic activity in the brain, a decrease in the concentration of the receptors was observed in the frontal cortex and hippocampus. On the other hand, when animals were subjected to daily 45-min exposure sessions that decreased cholinergic activity in the brain, an increase in the concentration of muscarinic cholinergic receptors in the hippocampus resulted after repeated exposure and no significant effect was observed in the frontal cortex. These data point to an important conclusion that the long term biological consequence of repeated RFR-exposure depend on the duration of each exposure session.

A series of experiments were performed to study the effects of RFR on benzodiazepine receptors in the brain. Benzodiazepine receptors are involved in anxiety and stress responses in animals [59] and have been shown to change after acute or repeated exposure to various 'stressors' [60, 61]. Exposure to RFR has been previously shown to affect the behavioral actions of benzodiazepines [62, 63]. After an acute (45 min) exposure to 2450-MHz RFR (average whole body SAR 0.6 W/kg), increase in the concentration of benzodiazepine receptors occurred in the cerebral cortex of the rat, but no significant effect was observed in the hippocampus and cerebellum. Furthermore, the response of the cerebral cortex adapted after repeated RFR exposure (ten 45-min sessions) [64]. Since benzodiazepine receptors are found in most regions of the brain

including the cerebral cortex and they can undergo changes after brief perturbation, it is possible that brief exposure to RFR from cellular telephones can lead to changes of these receptors in the cortex.

Data from the above experiments and those described in the previous sections indicate that the parameters of exposure are important determinants of the outcome of biological effects of RFR. Particularly, different durations of acute exposure could lead to different biological effects and, consequently, the effects of repeated exposure depend upon the duration of each exposure session.

Metabolic Changes in Neural Tissues

Metabolic changes in brain tissues have been reported after RFR exposure. Gandhi and Ross [65] reported that exposure of rat cerebral cortex synaptosomes to 2800-MHz RFR at power densities greater than $10 \, mW/cm^2$ (SAR, 1 mW/gm per mW/cm^2) increased ^{32}Pi incorporation into phosphoinositides. These phospholipids play an important role in membrane functions and act as second messengers in the transmission of neural information between neurons.

Several studies investigated the effects of RFR exposure on energy metabolism in the rat brain. Surprisingly, changes were reported after exposure to relatively low intensity RFR for a short duration of time (minutes). The effects depended on the frequency and modulation characteristics of the RFR and did not seem to be related to temperature changes in the tissue. Sanders and associates studied the components of the mitochrondrial electron transport system that generates high energy molecules for cellular functions. The compounds nicotinamide adenosine dinucleotide (NAD), adenosine triphosphate (ATP), and creatine phosphate (CP) were measured in the cerebral cortex of rats exposed to RFR. In one study, Sanders et al. [66] exposed the head of rats to 591-MHz continuous-wave RFR at 5.0 or 13.8 mW/cm^2 for 0.5-5 min (local SAR at the cortex of the brain was estimated to be between 0.026 and 0.16 W/kg per mW/cm^2). A decrease in concentrations of ATP and CP and an increase in NADH were observed in the cerebral cortex. These changes were found at both power densities of exposure. Furthermore, the researchers reported no significant change in cerebral cortical temperature at these power densities. They concluded that the radiation decreased the activity of the mitochrondrial electron transport system.

Sanders et al. [67] further tested the effect of different frequencies of radiation (200, 591 and 2450 MHz) on the mitochrondrial electron transport system. The effect on the concentration of NADH was found to be frequency dependent. An intensity-dependent

increase in NADH level was observed in the cerebral cortex when irradiated with the 200-MHz and 591-MHz radiations. No significant effect was seen with the 2450-MHz radiation.

In a further study [68], the effects of continuous-wave, sinusoidally amplitude-modulated, and pulsed 591-MHz RFR were compared after five minutes of exposure at power densities of 10 and 20 mW/cm^2 (SARs at the cerebral cortex were 1.8 and 3.6 W/kg). Different modulation frequencies (4-32 Hz) were used in the amplitude-modulation mode. There was no significant difference in the effect on the NADH level across these modulation frequencies. Furthermore, pulsed radiations of 250 and 500 pps (5 μs pulses) were compared with power densities ranging from 0.5-13.8 mW/cm^2. The 500 pps radiation was found to be significantly more effective in increasing the concentration of NADH in the cerebral cortex than the 250 pps radiation. Since changes in these experiments occurred when the tissue (cerebral cortex) temperature was normal, the authors speculated that they were not due to hyperthermia, but to a direct inhibition of the electron transport functions in the mitochrondria by RFR-induced dipole molecular oscillation in divalent metal containing enzymes or electron transport sites.

Another important topic of research on the neurochemical effect of RFR is the efflux of calcium ions from brain tissue. Calcium ions play important roles in the functions of the nervous system, such as the release of neurotransmitters and the actions of some neurotransmitter receptors. Thus, changes in calcium ion concentration could lead to alterations in neural functions. This is an area of considerable controversy because some researchers have also reported no significant effects of RFR exposure on calcium efflux (e.g., references 69,70). However, when positive effects were observed, they occurred after exposure to RFR of relatively low intensities and were dependent on the modulation and intensity of the RFR studied (window effects).

Bawin et al. [71] reported an increase in efflux of calcium ions from chick brain tissue after 20 min of exposure to a 147-MHz RFR (1 to 2 mW/cm^2). The effect occurred when the radiation was sinusoidally amplitude-modulated at 6, 9, 11, 16, or 20 Hz, but not at modulation frequencies of 0, 0.5, 3, 25, or 35 Hz. The effect was later also observed with 450-MHz radiation amplitude-modulated at 16 Hz, at a power density of 0.75 mW/cm^2.

In vitro increase in calcium efflux from the chick brain was further confirmed by Blackman et al. [72-75] using amplitude-modulated 147-MHz and 50-MHz RFR. They also reported both modulation-frequency and power windows. These data would argue against a role of temperature. The existence of a power-density window on calcium efflux was also reported by Sheppard et al. [76] using a 16-Hz amplitude-modulated 450-

MHz field. An increase in calcium ion efflux was observed in the chick brain irradiated at 0.1 and 1.0 mW/cm^2, but not at 0.05, 2.0, or 5.0 mW/cm^2.

Electromagnetic field-induced increases in calcium efflux have also been reported in tissues obtained from different species of animals. Adey et al. [77] observed an increase in calcium efflux from the brain of conscious cats paralyzed with gallamine and exposed for 60 min to a 450-MHz field (amplitude modulated at 16 Hz at 3.0 mW/cm^2, SAR 0.20 W/kg). Lin-Liu and Adey [78] also reported increased calcium efflux from synaptosomes prepared from the rat cerebral cortex when irradiated with a 450-MHz RFR amplitude-modulated at various frequencies (0.16-60 Hz). Again, modulation at 16 Hz was found to be the most effective. Dutta et al. [79] reported radiation-induced increases in calcium efflux from cultured cells of neural origins. Increases were found in human neuroblastoma cells irradiated with 915-MHz RFR (SARs 0.01-5.0 W/kg) amplitude-modulated at different frequencies (3-30 Hz). A modulation frequency window was reported. Interestingly, at certain power densities, an increase in calcium efflux was also seen with unmodulated radiation. A later paper by Dutta et al. [80] reported increased calcium efflux from human neuroblastoma cells exposed to 147-MHz RFR amplitude-modulated at 16 Hz. A power window (SAR between 0.05-0.005 W/kg) was observed. When the radiation at 0.05 W/kg was studied, peak effects were observed at modulation frequencies between 13-16 Hz and 57.5-60 Hz. In addition, these researchers also reported increased calcium efflux in another cell line, the Chinese hamster-mouse hybrid neuroblastoma cells. Effect was observed when these cells were irradiated with a 147-MHz radiation amplitude-modulated at 16 Hz (SAR 0.05 W/kg).

In further studies, Blackman explored the effects of different exposure conditions [81-83]. Multiple power windows of calcium efflux from chick brains were reported. Within the power densities studied in this experiment (0.75-14.7 mW/cm^2, SAR 0.36 mW/kg per mW/cm^2), narrow ranges of power density with positive effect were separated by gaps of no significant effect.

These studies on the effects of RFR on cellular metabolism are particularly interesting. Effects apparently can occur under low SARs of exposure and demonstrated both frequency and intensity windows. In addition, amplitude or frequency modulation of the RFR could also affect the response.

Cytogenetic Effects

Cytogenetic effects have been reported in various types of cells after exposure to RFR [84-89]. Recently, several studies have reported cytogenetic changes in brain cells

by RFR, and these results could have important indication on the health effects of RFR. Singh et al. [90] reported significant decreases in poly-ADP-ribosylation, a process involved in chromatin functions, in the brain of rats after sixty days of exposure to 2450-MHz RFR (1 mW/cm^2). Sarkar et al. [91] reported changes in DNA sequences in mouse brain cells after exposure to RFR (1 mW/cm^2, 2 hr/day for 120, 150, and 200 days). Lai and Singh [92] reported an increase in single strand DNA breaks in brain cells of rats after 2 hours of exposure to 2450-MHz RFR (whole body SAR 0.6 and 1.2 W/kg). Genetic damages to glial cells can result in carcinogenesis. However, since neurons do not undergo mitosis, a more likely consequence of neuronal genetic damage is changes in functions and cell death, which could either lead to or accelerate the development of neurodegenerative diseases. We have recently reported [93] an increase in DNA double strand breaks in brain cells of rats after acute exposure to RFR. Double strand breaks, if not probably repaired, is known to lead to cell death. Indeed, we have observed an increase in apoptosis (scheduled cell death) in cells exposed to RFR (unpublished results). This type of response would lead to an inverted-U response function in carinogenesis and may explain recent reports of increase [94], decrease [95], and no significant effect [96] on cancer rate of animals exposed to RFR.

Interestingly, RFR-induced increases in single and double strand DNA breaks can be blocked by treating the rats with melatonin or the spin-trap compound N-t-butyl-α-phenylnitrone [97]. Since both compounds are potent free radical scarvengers, this data suggest that free radicals may play a role in the genetic effect of RFR. If free radicals are involved in the RFR-induced DNA strand breaks in brain cells, results from this study could have an important implication on the health effects of RFR exposure. Involvement of free radicals in human diseases, such as cancer and atherosclerosis, have been suggested. Free radicals also play an important role in aging processes, which have been ascribed to be a consequence of accumulated oxidative damage to body tissues [98, 99], and involvement of free radicals in neurodegenerative diseases, such as Alzheimer's, Huntington, and Parkinson, has also been suggested [100,101]. Furthermore, the effect of free radicals could depend on the nutritional status of an individual, e.g., availability of dietary antioxidants [102], consumption of alcohol [103], and amount of food consumption [104]. Various life conditions, such as psychological stress [105] and strenuous physical exercise [106], have been shown to increase oxidative stress and enhance the effect of free radicals in the body. Thus, one can also speculate that some individuals may be more susceptible to the effects of RFR exposure.

Discussion

Existing data indicate that RFR of relatively low intensity (SAR < 2 W/kg) can affect the nervous system. Changes in blood-brain-barrier, morphology, electrophysiology, neurotransmitter functions, cellular metabolism, and calcium efflux, and genetic effects have been reported in the brain of animals after exposure to RFR. These changes can lead to functional changes in the nervous system. Behavioral changes in animals after exposure to RFR have been reported [see learning sections in reference 107].

Even a temporary change in neural functions after RFR exposure could, depending on the situation, lead to adverse consequences. For example, a transient loss of memory function or concentration could result in an accidence when a person is driving. Loss of short term working memory has indeed been observed in rats after acute exposure to RFR [108].

However, great caution should be taken in applying the existing research results to evaluate the possible effect of exposure to RFR during cellular telephone use. It is apparent that not enough research data is available to conclude whether exposure to RFR during the normal use of cellular telephones could lead to any hazardous health effect.

Data available suggest a complex reaction of the nervous system to RFR. The response is not likely to be linear with respect to the intensity of the radiation. Other parameters of RFR exposure, such as frequency, duration, waveform, frequency- and amplitude-modulation, etc, are also important determinants of biological responses and affect the shape of the dose(intensity)-response relationship. Some of the studies described above also suggested frequency and power window effects, i.e., effect is only observed at a certain range of frequency and intensity and not at higher or lower ranges; and dependency on the duration of individual exposure episodes. In order to understand the possible health effects of exposure to RFR from cellular telephones, one needs first to understand the effects of these different parameters and how they interact with each other.

Research has also shown that the effects of RFR on the nervous system can cumulate with repeated exposure. The important question is, after repeated exposure, will the nervous system adapt to the perturbation and when will homeostasis break down? Related to this is that various lines of evidence suggest that responses of the central nervous system to RFR could be a stress response [109]. Stress effects are well known to cumulate over time and involve first adaptation and then an eventual break down of homeostatic processes.

In conclusion, research is needed to investigate the effects of different RFR exposure parameters. Particularly, studies using RFR of frequencies and waveforms similar to those emitted from cellular telephones and intermittent exposure schedule resembling the normal pattern of phone use are needed.

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