NEUROLOGICAL EFFECTS OF RADIOFREQUENCY ELECTROMAGNETIC RADIATION

Henry Lai

Department of Pharmacology and Center for Bioengineering
University of Washington
Seattle, WA 98195

INTRODUCTION

Many reports in the literature have suggested the effect of exposure to radiofrequency electromagnetic radiation (RFR) (10 kHz-300,000 MHz) on the functions of the nervous system. Such effects are of great concern to researchers in bioelectromagnetics, since the nervous system coordinates and controls an organism's responses to the environment through autonomic and voluntary muscular movements and neurohumoral functions. As it was suggested in the early stages of bioelectromagnetics research, behavioral changes could be the most sensitive effects of RFR exposure. At the summary of session B of the proceedings of an international symposium held in Warsaw, Poland, in 1973, it was stated that "The reaction of the central nervous system to microwaves may serve as an early indicator of disturbances in regulatory functions of many systems" [Czerski et al., 1974].

Studies on the effects of RFR on the nervous system involve many aspects: morphology, electrophysiology, neurochemistry, neuropsychopharmacology, and psychology. An obvious effect of RFR on an organism is an increase in temperature in the tissue, which will trigger physiological and behavioral thermal regulatory responses. These responses involve neural activities both in the central and peripheral nervous systems. The effects of RFR on thermoregulation have been extensively studied and reviewed in the literature [Adair, 1983; Stern, 1980]. The topic of thermoregulation will not be reviewed in this chapter. Since this paper deals mainly with the effects of RFR on the central nervous system, the effect on neuroendocrine functions also will not be reviewed here. It is, however, an important area of research since disturbances in neuroendocrine functions are related to stress, alteration in immunological responses, and tumor development [Cotman et al., 1987; Dunn, 1989; Plotnikoff et al., 1991]. Excellent reviews of research on this topic have been written by Lu et al.[1980] and Michaelson and Lin [1987].

In order to give a concise review of the literature on the effects of RFR on neural functions, we have to first understand the normal functions of the nervous system.

PRINCIPLES OF NEURAL FUNCTIONS

The nervous system is functionally composed of nerve cells (neurons) and supporting cells known as glia. In higher animal species, it is divided into the central and peripheral nervous systems. The central nervous system consists of the brain and the spinal cord and is enveloped in a set of membranes known as the meninges. The outer surface as well as the

Advances in Electromagnetic Fields in Living Systems, Vol. 1
Edited by J.C. Lin, Plenum Press, New York, 1994

inner structures of the central nervous system are bathed in the cerebrospinal fluid (CSF) that fills the ventricles of the brain and the space at the core of the spinal cord.

The brain is generally subdivided into regions (areas) based on embryological origins. The anterior portion of the neural tube, the embryonic tissue from which the nervous system is developed, has three regions of expansion: the forebrain, midbrain, and hindbrain. From the forebrain, the cerebral hemispheres and the diencephalon will develop. The diencephalon consists of the thalamus, epithalamus, subthalamus, and hypothalamus. The midbrain remains mostly unchanged from the original structure of the neural tube; however, two pairs of structures, the superior and inferior colliculi, develop on its dorsal surface. These are parts of the visual and auditory systems, respectively. The hindbrain develops into the medulla, pons, and cerebellum.

The thalamus of the diencephalon is divided into various groups of cells (nuclei). Some of these nuclei are relays conveying sensory information from the environment to specific regions of the cerebral cortex, such as the lateral and medial geniculate nuclei that relay visual and auditory information, respectively, from the eyes and ears to the cerebral cortex. Other nuclei have more diffuse innervations to the cerebral cortex. The hypothalamus is involved in many physiological regulatory functions such as thermoregulation and control of secretion of hormones.

The cerebral hemispheres consist of the limbic system (including the olfactory bulbs, septal nucleus, amygdala, and hippocampus), the basal ganglia (striatum), and the cerebral cortex. The limbic system serves many behavioral functions such as emotion and memory. The striatum is primarily involved in motor controls and coordination. The cerebral cortex especially in the higher animal species is divided into regions by major sulci: frontal, parietal, temporal, and occipital cortex, etc. The function of some regions can be traced to the projection they receive from the thalamus, e.g., the occipital cortex (visual cortex) processes visual information it receives from the lateral geniculate nucleus of the thalamus and the temporal cortex (auditory cortex) receives auditory information from the medial geniculate nucleus. There are other cortical areas, however, known as secondary sensory areas and 'association' cortex that receive no specific thalamic innervations. One example of the association cortical areas is the prefrontal cortex, which is supposed to subserve higher behavioral functions, e.g., cognition.

The basic design of the central nervous system is similar among species in the phylogenetic scale; however, there are differences in the details of structure among species. Most of the brain regions mentioned in the above sections have been studied in bioelectromagnetics research to a various extent.

On the neurochemical level, neurons with similar biochemical characteristics are usually grouped together to form a nucleus or ganglion. Information is transmitted by electrochemical means via fibers (axons) protruding from the neuron. In addition to making local innervations to other neurons within the nucleus, nerve fibers from the neurons in a nucleus are also grouped into bundles (pathways) that connect one part of the brain to another. Information is generally passed from one neuron to another via the release of chemicals. These chemicals are called neurotransmitters or neuromodulators depending upon their functions. Many neurotransmitters have been identified in the central nervous system. Some are small molecules such as acetylcholine, norepinephrine, dopamine, serotonin, and γ–amino-butyric acid (GABA), whereas the others are polypeptides and proteins such as the endogenous opioids, substance-P, etc. Effects of RFR on most of these neurotransmitters have been investigated. Nerve fibers in a pathway usually release the same neurotransmitter. The anatomy of some of these neurotransmitter pathways are well studied such as those of dopamine, norepinephrine, serotonin, and acetylcholine.

After a neurotransmitter is released, it passes a space gap (synapse) between two adjacent cells and reacts with a molecule known as "receptor" at the cell membrane of the receiving (postsynaptic) cell. Such a reaction is usually described as analogous to the action

of the key and lock. A particular neurotransmitter can only bind to its specific receptor to exert an effect. Binding of the neurotransmitter to a receptor triggers a series of reactions that affect the postsynaptic cell. Properties of the receptors can be studied by the receptor-ligand binding technique. Using this method the concentration and the binding affinity to the neurotransmitter of the receptors in a neural tissue sample can be determined.

Pharmacologically, one can affect neural functions by altering the events of synaptic transmission by the administration of a drug. Drugs can be used to decrease or increase the release of neurotransmitters or affect the activity of the receptors. Many drugs exert their effects by binding to neurotransmitter receptors. Drugs which have actions at the receptors similar to those of the natural neurotransmitters are called agonists, whereas drugs which block the receptors (thus blocking the action of the endogenous neurotransmitters) are known as antagonists. The property of antagonists provides a powerful conceptual tool in the study of the functions of the nervous system. Neural functions depend on the release of a particular type of neurotransmitter. If a certain physiological or behavioral function is blocked by administration of a certain antagonist to an animal, one could infer that the particular neurotransmitter blocked by the antagonist is involved in the function. In addition, since neurons of the same chemical characteristics are grouped together into pathways in the nervous system, from the information obtained from the pharmacological study, one can speculate on the brain areas affected by a certain treatment such as RFR.

The activity in the synapses is dynamic. In many instances as a compensatory response to changes in transmission in the synapses, the properties (concentration and/or affinity) of the receptors change. Generally, as a result of repeated or prolonged increase in release of a neurotransmitter, the receptors of that neurotransmitter in the postsynaptic cells decrease in number or reduce their binding affinity to the neurotransmitter. The reverse is also true, i.e., increase in concentration or binding affinity of the receptors occurs after prolonged or repeated episodes of decreased synaptic transmission. Such changes could have important implications on an animal's functional state. The changes in neurotransmitter receptors enable an animal to adapt to the repeated perturbation of function. On the other hand, since changes in receptor properties can last for a long time (days to weeks), an animal's normal physiological and behavioral functions will be altered by such changes.

The central nervous system of all vertebrates is enveloped in a functional entity known as the blood-brain barrier, due to the presence of high-resistance tight junctions between endothelial cells in the capillaries of the brain and spinal cord. The blood-brain barrier is impermeable to hydrophilic (polar) and large molecules and serves as a protective barrier for the central nervous system against foreign and toxic substances. Many studies have been carried out to investigate whether RFR exposure affects the permeability of the blood-brain barrier.

Drugs can be designed that cannot pass through the blood-brain barrier and, thus, they can only affect the peripheral nervous system. Using similar antagonists that can and cannot pass through the blood-brain barrier, one can determine whether an effect of an entity such as RFR is mediated by the central or peripheral nervous system. On the other hand, drugs can be directly injected into the central nervous system (thus, by-passing the blood-brain barrier) to investigate the roles of neural mechanisms inside the brain on a certain physiological or behavioral function.

Changes in neurochemical functions lead to changes in behavior in an animal. Research has been carried out to investigate the effects of RFR exposure on spontaneous and learned behaviors. Motor activity is the most often studied spontaneous behavior. Alteration in motor activity of an animal is generally considered as an indication of behavioral arousal. For learned behavior, conditioned responses were mostly studied in bioelectromagnetics research. The behavior of an animal is constantly being modified by conditioning processes, which connect behavioral responses with events (stimuli) in the environment. Two types of conditioning processes have been identified and they are known as classical and operant

conditioning. In classical conditioning, a 'neutral' stimulus that does not naturally elicit a certain response is repeatedly being presented in sequence with a stimulus that does elicit that response. After repeated pairing, presentation of the neutral stimulus (now the conditioned stimulus) will elicit the response (now the conditioned response). Interestingly, the behavioral control probability of the conditioned stimulus is shared by similar stimuli, i.e., presentation of a stimulus similar to the conditioned stimulus can also elicit the conditioned response. The strength and probability of occurrence of the conditioned response depends on the degree of similarity between the two stimuli. This is known as "stimulus generalization."

A paradigm of classical conditioning used in bioelectromagnetics research is the "conditioned suppression" procedure. Generally, in this conditioning process, an aversive stimulus (such as electric shock, loud noise) follows a warning signal. After repeated pairing, the presentation of the warning signal alone can stop or decrease the on-going behavior of the animal. The animal usually "freezes" for several minutes and shows emotional responses like defecation and urination. Again, stimulus generalization to the warning signal can occur.

Operant (or instrumental) conditioning involves a change in the frequency or probability of a behavior by its consequences. Consequences which increase the rate of the behavior are known as "reinforcers". Presentation of a "positive reinforcer", e.g., availability of food to a hungry animal, increases the behavior leading to it. On the other hand, removal of a "negative reinforcer", e.g., an electric shock, also leads to an increase of the behavior preceding it. Presentation of an aversive stimulus will decrease the probability of the behavior leading to it. In addition, removal of a positive reinforcer contingent upon a response will also decrease the probability of further response. Thus, both positive and negative reinforcers increase the probability of a response leading to them, and punishment (presentation of an aversive stimulus or withdrawal of a positive reinforcer) decreases the occurrence of a response. The terms used to describe a consequence are defined by the experimental procedures. The same stimulus can be used as a "negative reinforcer" to increase a behavior or as a punisher to decrease the behavior.

An interesting aspect of behavioral conditioning is the schedule on which an animal is reinforced (schedule-controlled behavior). An animal can be reinforced for every response it emits; however, it can also be reinforced intermittently upon responding. Intermittent reinforcement schedules generally consist of the following: reinforcement is presented after a fixed number of responses (fixed ratio), a fixed period of time (fixed interval), or a variable number of responses (variable ratio) or interval of time (variable interval) around an average value. The intermittent reinforcement schedules have a profound effect on the rate and pattern of responding. The variable schedules generally produce a steadier responding rate than the fixed schedules. A post-reinforcement pulse is associated with the fixed schedules when the rate of responding decreases immediately after a reinforcement and then increases steadily. Ratio schedules generally produce a higher responding rate than interval schedules. Another simple reinforcement schedule commonly used in bioelectromagnetics research is the differential reinforcement of a low rate of responding (DRL). In this schedule, a reinforcement only follows a response separated from the preceding response by a specific time interval. If the animal responds within that time, the timer will be reset and the animal has to wait for another period of time before it can elicit a reinforceable response. The DRL schedule, dependent of the time interval set, produces a steady but low rate of responding. Compound schedules, consisting of two or more of the above schedule types, can also be used in conditioning experiments to control behavior. A multiple schedule is one in which each component is accompanied by a discriminatory stimulus, e.g., a white light when a fixed interval schedule is on and a green light when a variable interval schedule is on. The multiple schedule paradigm is widely used in pharmacological research to compare the effect of a drug on the patterns of response under different schedules in the same individual. A mixed schedule is a multiple schedule with no discriminative stimulus associated with each schedule component. Thus, a multiple schedule produces discrete patterns of responding,

depending on the currently active schedule, whereas a mixed schedule produces a response pattern that is a blend of all the different components. A tandem schedule consists of a sequence of schedules. Completion of one schedule leads to access to the next schedule, with no reinforcement presented until the entire sequence of schedules is completed. A chained schedule is a tandem schedule with each component accompanied by a discriminatory stimulus. Other more complicated combinations of schedules can be used in conditioning experiments. These compound schedules pose increased difficulties in an animal's ability to respond and make the performance more sensitive to the disturbance of experimental manipulations such as RFR.

In operant discrimination learning, an animal learns to elicit a certain response in the presence of a particular environmental stimulus, e.g., light, and is rewarded after the response, whereas no reinforcement is available in the absence of the stimulus or in the presence of another stimulus, e.g., tone. In this case, generalization to similar stimuli can also occur.

Another popular paradigm used in the research on the behavioral effects of RFR is escape and avoidance learning. In escape responding an animal elicits a response immediately when an aversive stimulus, e.g., electric foot-shock, is presented in order to escape from it or to turn it off. In avoidance learning an animal has to make a certain response to prevent the onset of an aversive stimulus. The avoidance can be a signalled avoidance-escape paradigm in which a stimulus precedes the aversive stimulus. On the other hand, the aversive stimulus can be nonsignalled. In this case the animal has to respond continuously to postpone the onset of the aversive stimulus, otherwise it will be presented at regular intervals. This paradigm is also known as "continuous-avoidance." It was speculated that avoidance learning was reinforced by reduction of a conditioned fear reaction [Mowrer, 1939; Solomon and Wynne, 1954]. In escape-avoidance learning both classical and operant conditioning processes are involved.

Use of reinforcement-schedules can generate orderly and reproducible behavioral patterns in animals, and thus, allows a systematic study of the effect of an independent variable, such as RFR. However, the underlying mechanisms by which different schedules affect behavior are poorly understood. The significance of studying schedule-controlled behavior has been discussed by Jenkins [1970] and Reynolds [1968]. In addition, de Lorge [1985] has written a concise and informative review and comments on the use of schedule-controlled behavior in the study of the behavioral effects of RFR.

In the following review on the effects of RFR on the central nervous system the concepts described above on the functions of the nervous system will apply.

EFFECTS OF RADIOFREQUENCY RADIATION ON THE MORPHOLOGY OF THE CENTRAL NERVOUS SYSTEM

Cellular Morphology

Radiofrequency radiation-induced morphological changes of the central nervous system are not expected except under relatively high intensity or prolonged exposure to the radiation. Such changes are not a necessary condition for alteration in neural functions after exposure to RFR. Early Russian studies [Gordon, 1970; Tolgskaya and Gordon, 1973] reported morphological changes in the brain of rats after 40 min of exposure to 3000- or 10000-MHz RFR at power densities varying from 40-100 mW/cm^2 (rectal temperature increased to 42-45 ^oC). Changes included hemorrhage, edema, and vacuolation formation in neurons. In these studies, changes in neuronal morphology were also reported in the rat brain after repeated exposure to RFR of lower power densities (3000 MHz, thirty-five 30-min sessions, <10

mW/cm^2, SAR 2 W/kg). Changes included neuronal cytoplasmic vacuolation, swelling and beading of axons, and a decrease in the number of dendritic spines. Albert and DeSantis [1975] also reported swollen neurons with dense cytoplasm and decreased rough endoplasmic reticulum and polyribosomes, indicative of decreased protein synthesis, in the hypothalamus and subthalamic region of the brain of hamsters exposed for 30 min to 24 h to continuous-wave 2450-MHz RFR at 50 mW/cm^2 (SAR 15 W/kg). No observable effect was seen in the thalamus, hippocampus, cerebellum, pons, and spinal cord. Recovery was seen at 6-10 days postexposure. In the same study, vacuolation of neurons was also reported in the hypothalamus of hamsters exposed to 2450-MHz RFR at 24 mW/cm^2 (SAR 7.5 W/kg) for 22 days (14 h/day). Similar effects of acute exposure were observed in a second study [Albert and DeSantis, 1976] when hamsters were exposed for 30-120 min to continuous-wave 1700-MHz RFR at either 10 (SAR 3 W/kg) or 25 mW/cm^2 (SAR 7.5 W/kg). The effects persisted even at 15 days postexposure.

Baranski [1972] reported edema and heat lesions in the brain of guinea pigs exposed in a single 3-h session to 3000-MHz RFR at a power density of 25 mW/cm^2 (SAR 3.75 W/kg). After repeated exposure (3 h/day for 30 days) to similar radiation, myelin degeneration and glial cell proliferation were reported in the brains of exposed guinea pigs (3.5 mW/cm^2, SAR 0.53 W/kg) and rabbits (5 mW/cm^2, SAR 0.75 W/kg). Pulsed (400 pps) RFR produced more pronounced effects in the guinea pigs than continuous-wave radiation of the same power density. Switzer and Mitchell [1977] also reported an increase in myelin figures (degeneration) of neurons in the brain of rats at 6 weeks after repeated (5 h/day, 5 day/week for 22 weeks) exposure to continuous-wave 2450-MHz RFR (SAR 2.3 W/kg). In another study [McKee et al., 1980], Chinese hamsters were exposed to continuous-wave 1700-MHz RFR at 10 or 25 mW/cm^2 (SARs 5 and 12.5 W/kg) for 30-120 min. Abnormal neurons were reported in the hypothalamus, hippocampus, and cerebral cortex of the animals after exposure. In addition, platelet aggregation and occlusion of some blood vessels in the brain were also reported.

Two studies investigated the effects of perinatal exposure to RFR on the development of Purkinje cells in the cerebellum. In the first study [Albert et al., 1981a], pregnant squirrel monkeys were exposed to continuous-wave 2450-MHz RFR (3 h/day, 5 days/week) at a power density of 10 mW/cm^2 (SAR 3.4 W/kg) and the offspring were similarly exposed for 9.5 months after birth. No significant change was observed in the number of Purkinje cells in the uvula areas of the cerebellum of the exposed animals compared to that of controls. In the second study, Albert et al. [1981b] studied the effects of prenatal, postnatal, and pre- and postnatal-RFR exposure on Purkinje cells in the cerebellum of the rat. In the prenatal exposure experiment, pregnant rats were exposed from 17-21 days of gestation to continuous-wave 2450-MHz RFR at 10 mW/cm^2 (SAR 2W/kg) for 21 h/day. The offspring were studied at 40 days postexposure. A decrease (-26%) in the concentration of Purkinje cells was observed in the cerebellum of the prenatally RFR-exposed rats. In the pre- and postnatal-exposure experiment, pregnant rats were exposed 4 h/day between the 16-21 days of gestation and their offspring were exposed for 90 days to continuous-wave 100-MHz RFR at 46 mW/cm^2 (SAR 2.77 W/kg). Cerebellum morphology was studied at 14 months post-exposure. A 13% decrease in Purkinje cell concentration was observed in the RFR-exposed rats. The changes observed in the pre- and perinatally-exposed rats seemed to be permanent, since the animals were studied more than a month postexposure. In the postnatal exposure experiment, 6-day old rat pups were exposed 7 h/day for 5 days to 2450-MHz RFR at 10 mW/cm^2 and their cerebella were studied immediately or at 40 days after exposure. A 25% decrease in Purkinje cell concentration was found in the cerebellum of rats studied immediately after exposure, whereas no significant effect was observed in the cerebellum at 40 days postexposure. Thus, the postnatal exposure effect was reversible. The authors suggested that RFR may affect the proliferative activity and migrational process of Purkinje cells during cerebellar development. In a further study [Albert and Sherif, 1988], 1- or 6-day old rat pups

were exposed to continuous-wave 2450-MHz RFR for 5 days (7 h/day, 10 mW/cm^2, SAR 2W/kg). Animals were killed one day after the exposure and morphology of their cerebellum was studied. The authors reported two times the number of deeply stained cells with dense nucleus in the external granular layer of the cerebellum. Examination with an electron microscope showed that the dense nuclei were filled with clumped chromatin. Extension and disintegration of nucleus, ruptured nuclear membrane, and vacuolization of the cytoplasm were observed in these cells. Some cells in the external granular layer normally die during development of the cerebellum; therefore, these data showed that postnatal RFR exposure increased the normal cell death. In the same study, disorderly arrays of rough endoplasmic reticulum were observed in the Purkinje cells of the exposed animals indicating an altered metabolic state in these cells.

Blood-Brain Barrier

Intensive research effort was undertaken to investigate whether RFR affected the permeability of the blood-brain barrier [Albert, 1979b; Justesen, 1980]. The blood-brain barrier blocks the entry of large and hydrophilic molecules in the general blood circulation from entering the central nervous system. Its permeability was shown to be affected by various treatments, e.g., electroconvulsive shock [Bolwig, 1988]. Variable results on the effects of RFR on blood-brain barrier permeability have been reported. A reason for this could be due to the difficulties in measuring and quantifying the effect [Blasberg, 1979].

Frey et al. [1975] 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. The dye was found mostly in the lateral and third ventricles of the brain. A similar but more pronounced effect was observed when the animals were exposed to pulsed 1200-MHz RFR at an average power density of 0.2 mW/cm^2. These data were interpreted as an indication of an increase in permeability of the blood-brain barrier, since fluorescein injected systemically does not normally permeate into the brain. On the other hand, Merritt et al. [1978] did not observe a significant change in the permeability of fluorescein-albumin into the brain of rats exposed to a similar dose-rate of RFR (1200 MHz, either continuous-wave or pulsed, 30 min, 2-75 mW/cm^2); however, an increase in permeability was observed, if the body temperature of the animal was raised to 40 ^{o}C either by RFR or convective heating. In addition, no significant change in permeability of mannitol and inulin to the brain was reported in this experiment after RFR exposure.

Chang et al. [1982] studied in the dog the penetration of ^{131}I-labelled 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 and the tracer was injected intravenously. Radioactivity in the blood and cerebrospinal fluid (CSF) was determined at regular time intervals postinjection. An increase in the ratio of radioactivity in the CSF versus that in the blood was considered as an indication of entry of the labelled albumin that normally does not cross the blood-brain barrier. At 30 mW/cm^2, 4 of the 11 dogs studied showed a significant increase in the ratio compared to that of sham-exposed animals, whereas no significant difference was seen at the other power densities. The authors suggested a possible 'power window' effect.

Lin and Lin [1980] 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 after similar exposure of the head at an SAR of 240 W/kg [Lin and Lin, 1982]. The brain temperature under the latter exposure condition was 43 ^{o}C. In a further study, by the same laboratory, Goldman et al. [1984] used ^{86}Rb as the tracer to study the permeability of the blood-brain barrier after RFR exposure. The tracer was injected intravenously to rats after 5, 10, or 20 min of exposure to 2450-MHz pulsed RFR (10 μs pulses, 500 pps) at an average power density of 3 W/cm^2 (SAR 240 W/kg) on the left side of the head. Brain

temperature was increased to 43 °C. The ^{86}Rb uptake in the left hemisphere of the brain was studied. Increase in uptake was detected in the hypothalamus, striatum, midbrain, dorsal hippocampus, and occipital and parietal cortex at 5 min postexposure. Increased uptake of the tracer in the cerebellum and superior colliculus was also observed at 20 min after exposure. 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 [1986]. They showed that ethanol, infused into the femoral vein, reduced the RFR-induced (3150 MHz, 30 W/cm^2 rms for 15 min on the left hemisphere of the brain) increase in penetration of Evan's blue into the brain of rats. Ethanol attenuated the RFR-induced increase in brain temperature.

Several studies used horseradish peroxidase as an indicator of blood-brain barrier permeability. An increase in horseradish peroxidase in the brain after systemic administration could be due to an increase in pinocytosis of the epithelial cells in the capillary of the brain, in addition to or instead of an increase in the leakiness of the blood-brain barrier. Pinocytosis can actively transport the peroxidase from the general blood circulation into the brain. An increase in the concentration of horseradish peroxidase was found in the brain of the Chinese hamster after 2 h of irradiation to continuous-wave 2450-MHz RFR at 10 mW/cm^2 (SAR 2.5 W/kg) [Albert, 1977]. The increase was more concentrated in the thalamus, hypothalamus, medulla, and cerebellum, and less in the cerebral cortex and hippocampus [Albert and Kerns, 1981]. Increases in horseradish peroxidase permeability were also observed in the brains of rats and Chinese hamsters exposed for 2 h 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). Fewer brain areas were observed with horseradish peroxidase at 1 h postexposure and complete recovery was seen at 2 h [Albert, 1979a]. Sutton and Carroll [1979] also reported an increase in permeability of horseradish peroxidase to the brain of the rat, when the brain temperature was raised to 40-45 °C 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 the radiation. These results again point to the conclusion that the hyperthermic effect of the RFR can disrupt the blood-brain barrier.

Oscar and Hawkins [1977] reported increased permeability of radioactive mannitol and inulin, and no significant change in dextran 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). Effect of the pulsed radiation was more prominent. A 'power window' effect was also reported in this study. Preston et al. [1979] exposed rats to continuous-wave 2450-MHz RFR for 30 min at different power densities (0.1-30 mW/cm^2, SARs 0.02-6 W/kg) and observed no significant change in radioactive mannitol distribution in various regions of the brain. In that paper, they suggested that an increase in regional blood flow in the brain could explain the results of Oscar and Hawkins [1977]. In further experiments Preston and Prefontaine [1980] reported no significant change in the permeability of radioactive sucrose to the brain of rats exposed with the whole body to continuous-wave 2450-MHz RFR for 30 min at 1 or 10 mW/cm^2 (SARs 0.2 and 2.0 W/kg) or with the head for 25 min at different power densities. Gruenau et al. [1982] also reported no significant change on the penetration of ^{14}C-sucrose into the brain of rats after 30 min of exposure to pulsed (2 μs pulses, 500 pps) 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. [1982] 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 ^3H-inulin and ^{14}C-sucrose into different areas of the brain. Ambient temperature of exposure was at either 22, 30, or 40 °C. They reported no significant increase in penetration of both compounds into the brain due to RFR exposure; however, they reported an increase in ^{14}C-sucrose entry into the hypothalamus when the ambient temperature of exposure was at 40 °C. The increase was suggested to be due to the hyperthermia induced in the animals under such exposure conditions. In a further study,

Ward and Ali [1985] exposed rats to 1700-MHz continuous-wave or pulsed (0.5 μs pulses, 1000 pps) 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.

Oscar et al. [1981] did observe 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/cm^2 (SARs 0.2 and 3 W/kg). At 1 mW/cm^2, increased blood flow (measured at ~6 min after exposure) was observed in 16 of the 20 brain areas studied with the largest increase in the pineal gland, hypothalamus, and temporal cortex. After exposure to the radiation at 15 mW/cm^2, the largest increases in blood flow were detected in the pineal gland, inferior colliculus, medial geniculate nucleus, and temporal cortex (the last three areas are parts of the auditory system). It is interesting that patterns of changes involving different brain areas are reported in different studies [Albert and Kerns, 1981; Goldman et al., 1984; Oscar et al., 1981]. One wonders if this is due to the different patterns of energy distribution in the brain leading to different patterns of increases in local cerebral blood flow, since different exposure conditions were used in these experiments.

Williams et al. [1984a-d] carried out a series of experiments to study the effect of RFR exposure on blood-brain barrier permeability to hydrophilic molecules. Unrestrained, conscious rats were used in these studies. 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 ^{o}C)-induced hyperthermia and urea infusion, on sodium fluorescein, horseradish peroxidase, and ^{14}C-sucrose permeability into different areas of the brain. In general, they found that hyperosmolar urea was the most effective and ambient heating was as effective as hyperthermic RFR in increasing the tracer concentrations in the brain. However, significant increase of plasma concentrations of sodium fluorescein and ^{14}C-sucrose were also observed in the heat- and RFR-exposed animals, which might result from a decrease in renal function due to hyperthermia. Increase in tracer concentrations in the brain could be due to the increase in plasma concentrations. The authors concluded that RFR did not significantly affect the penetration of the tracers into the brain (via the blood-brain barrier). In the case of horseradish peroxidase, a reduced uptake into the brain was actually observed. The authors speculated that there was a decrease in pinocytotic activity in cerebral micro-vessels after exposure for 30 to 90 min to the radiation at 65 mW/cm^2.

A series of experiments was carried out to study the effect of RFR on the passage of drugs into the central nervous system. Drug molecules that are less lipid soluble are less permeable through the blood-brain barrier. Thus, their actions are confined mainly to the peripheral nervous system after systemic administration. The actions of methylatropine, a peripheral cholinergic antagonist, methylnaltrexone, a peripheral opiate antagonist, and domperidone, a peripheral dopamine antagonist on RFR-exposed rats were studied by Quock et al. [1986a,b; 1987]. After 10 min of irradiation of mice to continuous-wave 2450-MHz RFR at 20 mW/cm^2 (SAR 53 W/kg), they observed antagonism of the apomorphine (a dopamine agonist)-induced stereotypic climbing behavior by domperidone, the analgesic effect of morphine (an opiate) by methylnaltrexone, and the central effects of oxotremorine and pilocarpine (both cholinergic agonists) by methylatropine. The behavioral and physiological responses studied are due to the action of the agonists in the central nervous system and are normally not blocked by the peripheral antagonists used in these studies. Since the enhanced antagonist effects of the peripheral drugs cannot be due to an increase in cerebral blood flow after exposure to the RFR, Quock et al. [1986a] speculated that the effect may be due to the breakdown of capillary endothelial tight-junction or an increase in pinocytosis in the blood-brain barrier.

Neubauer et al. [1990] studied the penetration of rhodamine-ferritin complex into the blood-brain barrier of the rat. The compound was administered systemically to the animals and then the animals were irradiated with pulsed 2450-MHz RFR (10 μs pulses, 100 pps) for

15, 30, 60 or 120 min at an average power density of 5 or 10 mW/cm^2 (SAR of 2 W/kg). Capillary endothelial cells from the cerebral cortex of the rats were isolated immediately after exposure, and the presence of rhodamine-ferritin complex in the cells was determined by the fluorescence technique. An approximately two fold increase in the complex was found in the cells of animals after 30 min or more of exposure to the 10 mW/cm^2 radiation. No significant effect was observed at 5 mW/cm^2. Furthermore, pretreating the animals before exposure with the microtubular function inhibitor colchicine blocked the effect of the RFR. These data indicate an increase in pinocytotic activity in the cells forming the blood-brain barrier. In a more recent study [Lange and Sedmak, 1991], using a similar exposure system, a dose-(power density) dependent increase in the entry of Japanese encephalitis virus into the brain and lethality was reported in mice after 10 min of RFR exposure (power densities 10-50 mW/cm^2, SARs 24-98 W/kg). The blood-brain barrier is a natural barrier against the penetration of this virus to the brain. The authors also speculated that the high-intensity RFR caused an increase in pinocytosis of the capillary endothelial cells in the central nervous system and the viruses were carried inside by this process.

It is apparent that in the majority of the studies a high intensity of RFR is required to alter the permeability of the blood-brain barrier. Change in brain or body temperature seems to be a necessary condition for the effect to occur. In addition, permeability alteration could be due to a passive change in 'leakiness' or an increase in pinocytosis in the blood-brain barrier.

ELECTROPHYSIOLOGICAL EFFECTS OF RADIOFREQUENCY RADIATION

Electrophysiology of Neurons

Wachtel et al. [1975] and Seaman and Wachtel [1978] described a series of experiments investigating the effect of RFR (1500 and 2400 MHz) on neurons from the isolated abdominal ganglion of the marine gastropod, Aphysia. Two types of cells generating regular action potential spikes or bursts were studied. A majority of cells (87%) showed a decrease in the rate of the spontaneous activity when they were irradiated with RFR. 'Temperature' controls were run and in certain neurons convective warming produced an opposite effect (increased rate of activity) to that produced by RFR (decreased activity). Chou and Guy [1978] 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 these nerve preparations during exposure to either continuous-wave (SARs 0.3-1500 W/kg) or pulsed (peak SARs 0.3-220 W/kg) radiation. No direct field stimulation of neural activity was observed.

Arber and Lin [1985] 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 ^{o}C, but not at 28 ^{o}C. However, 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.

Evoked Potentials

Several studies investigated the effects of RFR on evoked potentials in different brain areas. The evoked potential is the electrical activity in a specific location within the central nervous system responding to stimulation of the peripheral nervous system. Johnson and Guy [1972] recorded the evoked potential in the thalamus of cats in response to stimulation of

the contralateral forepaw. The animals were exposed 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 components, but not the initial response of the thalamic evoked potential was observed. These data were interpreted that RFR affected the multisynaptic neural pathway, which relates neural information from the skin to the thalamus and is responsible for the late components of the evoked potential. Interestingly, warming the body of the animals decreased the latency of both the initial and late components of the evoked potential.

Taylor and Ashleman [1975] recorded spinal cord ventral root responses to electrical stimulation of the ipsilateral gastrocnemius nerve in cats, using a polyethylene suction electrode. 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.

Electrophysiology of Auditory Effect of Pulsed RFR

Electrophysiological methods have also been used to study the pulsed RFR-induced auditory effects in animals. The effect was first systemically studied in humans by Frey [1961] and has been reviewed by Chou et al. [1982a] and Lin [1978]. Evoked potential responses were recorded in the eighth cranial nerve, medial geniculate nucleus, and the primary auditory cortex (three components of the auditory system) in cats exposed to pulsed 2450-MHz RFR. These evoked responses were eliminated after damaging the cochlea [Taylor and Ashleman, 1974]. Guy et al. [1975] studied the threshold of evoked responses in the medial geniculate nucleus in the cat in response to pulsed RFR while background noise (50-15000 Hz, 60-80 dB) was used to interfere with the response. They reported that background noise did not significantly affect the threshold to the RFR response, but caused a large increase in threshold to sound stimulus applied to the ear. The authors speculated that RFR interacts with the high frequency component of the auditory response system. In the study, evoked potentials in brain sites other than those of the auditory system were also recorded during pulsed RFR stimulation.

Chou et al. [1975] confirmed the peripheral site of the auditory effect generation. They recorded cochlear microphonics in the guinea pig inner ear during stimulation with 918-MHz pulsed RFR. The response was similar in characteristics to the cochlear microphonics generated by a click. These data were further supplemented by the finding that the middle-ear was not involved in the pulsed RFR-induced auditory responses, since destruction of the middle ear did not abolish the RFR-induced evoked potential in the brainstem [Chou and Galambos, 1979].

Experiments [Chou and Guy, 1979b] studying the threshold of RFR auditory effect in guinea pigs using the brainstem auditory evoked responses showed that the threshold for pulses with pulse width less than 30 μs was related to the incident energy per pulse, and for larger duration pulses it was related to the peak power. In another study Chou et al. [1985b] measured the intensity-response relationship of brainstem auditory evoked response in rats exposed to 2450-MHz pulsed RFR (10 pps) of different intensities and pulse widths (1-10 μs) in a circularly polarized waveguide. They also confirmed in the rat that the response is dependent on the energy per pulse and independent of the pulse width (up to 10 μs in this experiment).

Lebovitz and Seaman [1977a,b] recorded responses from single auditory neurons in the auditory nerve of the cat in response to 915-MHz pulsed RFR. Responses are similar to those elicited by acoustic stimuli. Seaman and Lebovitz [1987; 1989] also recorded in the cat the responses of single neurons in the cochlear nucleus, a relay nucleus in the auditory system, to

pulsed 915-MHz RFR applied to the head of the animal. The threshold of response to RFR pulses was determined and found to be low (SAR response threshold determined at the midline of the brain stem, where the cochlear nucleus is located, was 11.1 mW/g/pulse corresponding to a specific absorption threshold of 0.6 μJ/g/pulse.)

Electroencephalographic Recording

Various experiments studied the effects of acute and chronic RFR exposures on electroencephalograph (EEG). Measurement of electrical activity from the brain using external electrodes provides a non-invasive means of studying brain activity. Electroencephalograph is the summation of neural activities in the brain and provides a gross indicator of brain functions. It is generated by cell activity in the cerebral cortex around the area of recording, but it is modulated by subcortical input, e.g., from the thalamus. Sophisticated techniques and methods are available in the recording and analysis of EEG that provide useful knowledge on brain functions [da Silva, 1991].

In the early studies on the effects of RFR on EEG, metal electrodes were used in recording that distorted the field and possibly led to artifactual results [Johnson and Guy, 1972]. Saline filled glass electrodes [Johnson and Guy, 1972] and carbon loaded Teflon electrodes [Chou and Guy, 1979a] were used in later experiments to record the electrical activity in the brain of animals during RFR exposure. The carbon loaded Teflon electrode has conductivity similar to tissue and, thus, minimizes field perturbation. It can be used for chronic EEG and evoked potential measurements in RFR studies.

Baranski and Edelwejn [1968] 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 h), desynchronization (arousal) was seen in the EEG after phenobarbital administration, whereas synchronization (sedation) was observed in the controls [Baranski and Edelwejn, 1974]. Goldstein and Sisko [1974] 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. [1975] 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.

Dumansky and Shandala [1974] reported in the rat and rabbit that changes in EEG rhythm occurred after chronic RFR exposure (120 days, 8 h/day) using a range of power densities. The authors 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. [1979] exposed rabbits to 2375-MHz RFR (0.01-0.5 mW/cm^2) 7 h/day for 3 months. Metallic electrodes were implanted in various regions of the brain (both subcortical and cortical areas) for electrical recording during the exposure period and postexposure. After 1 month of exposure at 0.1 mW/cm^2, the authors 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.

Bawin et al. [1973] 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.

Takashima et al. [1979] 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 h, field strength 60-500 V_{rms}/m) elicited no observable effect. Chronic exposure (2 h/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 an experiment by Chou and Guy [1979a], no significant change in electrical activity from the hypothalamus was detected in rabbits exposed to 2450-MHz RFR at 100 mW/cm^2 (SAR at electrode ~25 W/kg). In a chronic exposure experiment, Chou et al. [1982b] exposed rabbits to continuous-wave 2450-MHz RFR at 1.5 mW/cm^2 (2 h/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. They 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 exposure.

In a more recent study, Chizhenkova [1988] 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) using glass electrodes. She reported that RFR increased the incident of slow wave and spindles in the EEG, which are characteristics of slow wave sleep in animals. However, the radiation facilitated light-evoked responses in the visual cortex. Cells in the visual cortex also showed changes in firing rates (increase or decrease depending on the neuron studied). Driving responses of visual cortical neurons to light flashes, i.e., responses to sequence of light flashes of increasing frequency, were also enhanced by the RFR exposure. The author interpreted the data as showing a decrease in the threshold of visual evoked potential and an increase in excitability of visual cortical cells as a result of RFR exposure.

NEUROCHEMICAL EFFECTS OF RADIOFREQUENCY RADIATION

Neurochemical studies of RFR include those on the concentrations and functions of neurotransmitters, receptor properties, energy metabolism, and calcium efflux from brain tissues.

Changes in Neurotransmitter Functions

In most studies on the effects of RFR on neurotransmitter functions, only the concentration of neurotransmitters (usually measured as amount/gm wet weight of brain tissue) was measured in the brains of animals after irradiation. Data on change in concentration alone tells little about the nature of the effect, since it could result from different causes. For example, a decrease in the concentration could be due to an enhanced release or a decrease in synthesis of the neurotransmitter as the result of RFR exposure. For a more informative study, the turnover rate of a neurotransmitter should be investigated. This involves the measurement of the rate of decrease in concentration of the neurotransmitter when its synthesis is blocked and/or the rate of accumulation of the metabolites of the neurotransmitter. More recently, the rate of release of a neurotransmitter from a local brain region can be studied by the microdialysis technique.

Snyder [1971] reported a significant increase in the concentrations of serotonin and its metabolite, 5-hydroxyindolacetic acid, in the brain of rats after 1 h of exposure to continuous-wave 3000-MHz RFR at 40 mW/cm^2 (SAR 8 W/kg). However, decreases in both neuro-

chemicals were observed in the brain of rats exposed 8 h/day for 7 days at 10 mW/cm^2. Thus, these results indicated an increase in the synthesis and turnover of brain serotonin after acute exposure and a decrease after prolonged exposure to RFR. Furthermore, warming the animals by placing them in an incubator heated at 34 °C had no significant effect on the turnover rate of serotonin in the brain.

Catravas et al. [1976] also reported an increase in diencephalon serotonin concentration and activity of tryptophan hydroxylase, the synthesis enzyme for serotonin, in the rat after 8 daily (8 h/day) exposures to RFR at 10 mW/cm^2. No significant changes in activity of monoamine oxidase, the degradation enzyme of serotonin, was observed in the brain of the irradiated rats.

Zeman et al. [1973] investigated the effects of exposure to pulsed 2860-MHz RFR on γ-amino-butyric acid (GABA) in the rat brain. No significant difference was observed in GABA concentration nor the activity of its synthesis enzyme, L-glutamate decarboxylase, in the brains of chronic (10 mW/cm^2, 8 h/day for 3-5 days, or 4 h/day, 5 days/week for 4 or 8 weeks) or acutely exposed (40 mW/cm^2 for 20 min, or 80 mW/cm^2 for 5 min) rats compared with those of the sham-exposed animals.

Rats exposed to continuous-wave 1600-MHz RFR at 30 mW/cm^2 for 10 min were reported to have altered concentrations of catecholamines (norepinephrine and dopamine) and serotonin in specific regions of the brain [Merritt et al., 1976]. Norepinephrine was decreased only in the hypothalamus, whereas decrease in serotonin was seen in the hippocampus and decreases in dopamine were observed in the striatum and hypothalamus. These effects were suggested to be caused by an uneven distribution of RFR in different regions of the brain. In a further study, rats exposed to similar radiation (20 or 80 mW/cm^2) were found to have a reduction of norepinephrine concentration in the basal hypothalamus, whereas no significant changes in dopamine and serotonin concentrations were observed even though the brain temperature increased up to 5 °C [Merritt et al., 1977]. In another study [Grin, 1974], rats were exposed to 2375-MHz RFR at power densities of 50 and 500 μW/cm^2 for 30 days (7 h/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 at day 5, but declined continually after further exposure.

Various studies have been carried out to investigate the neurochemical effects of RFR irradiation on acetylcholine in the brain. A decrease in whole brain concentration of acetylcholine, suggesting an increased release of the neurotransmitter, has been reported in mice exposed to a single 2450-MHz RFR pulse, which deposited 18.7 J in the brain and increased the brain temperature by 2 to 4 °C [Modak et al., 1981]. Several studies investigated the effect on acetylcholinesterase (AChE), the degradation enzyme for acetylcholine. Acute (30 min) exposure to 9700-MHz RFR was reported to inhibit the membrane-bound AChE activity in a vagal-heart preparation [Young, 1980]. This effect was attributed to a release of bound calcium from the postjunctional membrane. In another study [Baranski, 1972], acute exposure to pulsed RFR (~3000 MHz) at 25 mW/cm^2 caused a decrease in AChE activity in the guinea pig brain. The effect was most pronounced at the diencephalon and mesencephalon (midbrain). After three months (3 h/day) of exposure at a power density of 3.5 mW/cm^2, an increase in brain AChE was observed. Surprisingly, when rabbits were subjected to the same chronic exposure treatment, a decrease in AChE activity was seen. On the other hand, two groups of investigators [Galvin et al., 1981; Miller et al., 1984] showed independently that 2450-MHz RFR exposure at a wide range of SARs did not significantly affect the activity of isolated AChE in vitro. More recently, Dutta et al. [1992] 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. The authors suggested a 'power window' effect. It is not known whether the effect was a response to the radiofrequency or the 16-Hz component of the radiation.

Acetylcholinesterase is a very effective enzyme. A large decrease in its activity will be needed before any change in cholinergic functions can be observed.

D'Inzeo et al. [1988] reported an experiment that showed the direct action of RFR on acetylcholine-related ion channels in cultured chick embryo myotube cells. The acetylcholine-induced opening and closing of a single channel in the membrane of these cells were studied by the patch-clamp technique. Changes in membrane current of the whole cell in response to acetylcholine was also studied. The channels were probably the nicotinic cholinergic receptor channels, which are ligand-gated channels. 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 $\mu W/cm^2$.) Recordings were made during exposure. The authors reported a decrease in acetylcholine-activated single channel opening, whereas the duration of channel opening and the conductance of the channels were not significantly affected by the radiation. Since these latter two parameters are temperature-dependent, the effect observed was suggested as not related to the thermal effects of RFR. The whole cell membrane current also showed an increase in the recovery rates (desensitization) during irradiation. Thus, RFR decreased the opening probability of the acetylcholine channel and increased the rate of desensitization of the acetylcholine receptors. Opening and desensitization of the nicotinic channels are known to involve different molecular mechanisms.

Lai et al. [1987b,c] 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, were studied. The former pathway has the cell bodies in the septum and their axons innervate the hippocampus. The latter pathway includes neurons in the nucleus basalis and innervates several cortical areas including the frontal cortex. These two cholinergic pathways are involved in many behavioral functions such as learning, memory, and arousal [Steriade and Biesold, 1990]. Degeneration of these pathways occurs in Alzheimers disease [Price et al., 1985]. In some studies, cholinergic activities in the striatum and hypothalamus were also investigated. Cholinergic activity in the brain tissue was monitored by measuring sodium-dependent high-affinity choline uptake (HACU) from brain tissues. Sodium-dependent high-affinity choline is the rate limiting step in the synthesis of acetylcholine and has widely been used as an index of cholinergic activity in neural tissue [Atweh et al., 1975].

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 [Lai et al., 1987b]. Interestingly, the effect of RFR on HACU in the hippocampus was blocked by pretreatment of the animals with the opiate-antagonists naloxone and naltrexone, suggesting involvement of endogenous opioids in the effect. Endogenous opioids are a group of peptides synthesized by the nervous system and have pharmacological properties like opiates. They are involved in a variety of physiological functions such as stress reactions, temperature-regulation, motivational behaviors, etc. Our further research showed that the effects of RFR on central cholinergic activity could be classically conditioned to cues in the exposure environment [Lai et al., 1987c]. These effects of RFR on cholinergic functions are similar to those reported in animals after exposure to stressors [Finkelstein et al., 1985; Lai, 1987; Lai et al., 1986c].

When different power densities of RFR were used, a dose-response relationship could be established from each brain region [Lai et al., 1989a]. 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 required 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 further 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. 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 [Lai et al., 1989b], and these effects could be blocked by pretreatment with the opiate antagonist naltrexone, suggesting the effects are also mediated by endogenous opioids.

Experiments [Lai et al., 1988] were then carried out to compare the effects of exposure in two different systems that produced different energy absorption patterns in the body of the exposed animal. Rats were exposed to pulsed (2 μs pulses, 500 pps) or continuous-wave 2450-MHz RFR in the circular waveguide and the miniature anechoic chamber exposure systems designed by Guy [Guy, 1979; Guy et al., 1979] with the whole body average SAR kept at a constant level of 0.6 W/kg. In the circular waveguide rats were exposed to circularly polarized RFR from the side of the body. In the miniature anechoic chamber rats were exposed dorsally with plane-polarized RFR. The circular waveguide produced a more localized energy absorption pattern than the miniature anechoic chamber. Detailed dosimetry studies in the body and brain of rats exposed in these two exposure systems had been carried out [Chou et al., 1984, 1985a]. After 45 min of exposure to the RFR, a decrease in HACU was observed in the frontal cortex in all exposure conditions studied (circular waveguide vs miniature anechoic chamber, pulsed vs continuous-wave). However, regardless of the exposure system used, HACU in the hippocampus decreased only after exposure to pulsed, but not continuous-wave RFR. Striatal HACU was decreased after exposure to either pulsed or continuous-wave RFR in the miniature anechoic chamber, but no significant effect was observed when the animal was exposed in the circular waveguide. No significant effect on HACU was found in the hypothalamus under all the exposure conditions studied. Thus, each brain region responded differently to RFR exposure depending on the parameters. Effects on the frontal cortex were independent of the exposure system or use of pulsed or continuous-wave RFR. The hippocampus only responded to pulsed but not to continuous-wave RFR. Response of the striatum depended on the exposure system used. The neurochemical changes were correlated with the dosimetry data of Chou et al. [1985a] on the local SARs in different brain areas of rats exposed to RFR in these two exposure systems. The dosimetry data showed that the septum, where the cell bodies of the hippocampal cholinergic pathway are located, had the lowest local SAR among eight brain areas measured in both exposure systems; however, the hippocampus cholinergic pathway responded to pulsed, but not to continuous-wave RFR. Dosimetry data from the frontal cortex showed a wide range of local SARs in the frontal cortex (0.11-1.85 W/kg per $mW/cm^{2)}$ depending on the exposure system. Yet, exposure in both systems produced similar neurochemical responses in the frontal cortex (30-40% decrease in HACU). More interestingly, in the striatum the local SAR was approximately five times higher when the animals were exposed in the circular waveguide than in the miniature anechoic chamber; however, the striatal cholinergic system responded when the animal was exposed in the miniature anechoic chamber, but not in the circular waveguide. Since the cholinergic innervations in the striatum are mostly from interneurons inside the brain structure, these data would argue against a direct action of RFR on striatal cholinergic neurons causing a decrease in HACU, e.g., a local heating by the radiation. Unless different brain areas have different sensitivities to the direct effect of RFR, we could conclude that the effects of RFR on HACU in the brain areas studied in our experiments originated from other sites in the brain or body.

Neurotransmitter Receptors

Further experiments were conducted to investigate the effects of repeated RFR exposure on the cholinergic systems in the brain. Muscarinic cholinergic receptors were studied using

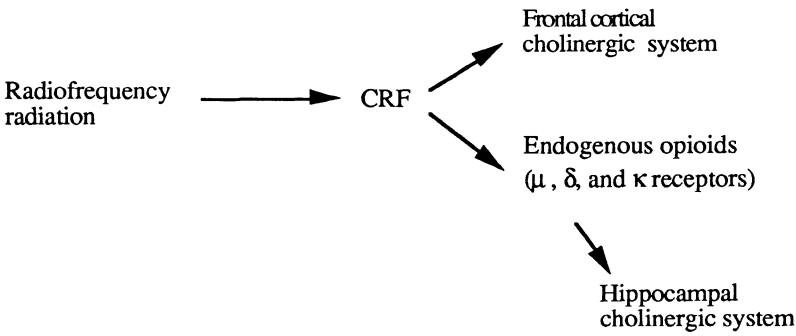
the receptor-binding technique with ^{3}H-quinuclidinyl benzilate (QNB) as the ligand. These receptors are known to change their properties after repeated perturbation of the cholinergic system and that such changes can affect an animal's normal physiological functions [Overstreet and Yamamura, 1979]. 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 [Lai et al., 1989b]. Moreover, 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 pointed to an important conclusion that the long term biological consequence of repeated RFR-exposure depended on the parameters of exposure. Further experiments showed that changes in cholinergic receptors in the brain after repeated RFR exposure also depended on endogenous opioids, because the effects could be blocked by pretreatment before each session of daily exposure with the narcotic antagonist naltrexone [Lai et al., 1991]. Interestingly, changes in neurotransmitter receptor concentration also have been reported in animals after a single episode of exposure to RFR [Gandhi and Ross, 1987]. In the experiment rats were irradiated with 700-MHz RFR at 15 mW/cm^2 to produce a rise in body temperature of 2.5 ^{o}C (~10 min) and in some animals the temperature was allowed to return to normal (~50 min). Alpha-adrenergic and muscarinic cholinergic receptors were assayed in different regions of the brain using ^{3}H-clonidine and ^{3}H-QNB as ligands, respectively. No significant change in binding was observed for both receptors studied at the time when the body temperature reached a 2.5 ^{o}C increase. Decreases in ^{3}H-clonidine binding in the cerebral cortex, hypothalamus, striatum, and hypothalamus, and an increase in ^{3}H-QNB binding in the hypothalamus were observed when the brains were studied at the time the body temperature returned to the base line level. The authors speculated that the receptor changes were thermoregulatory responses to the hyperthermia. It is not uncommon that the concentration of neurotransmitter receptors in the brain changes after a single exposure to drug or perturbation, e.g., stress [Estevez et al., 1984; Mizukawa et al., 1989].

Data from the above experiments and those described in the previous section indicate that the parameters of irradiation are important determinants of the outcome of the biological effect. Different durations of acute exposure lead to different biological effects and, consequently, the effects of repeated exposure depends upon the duration of each exposure session. On the other hand, the waveform of the irradiation was an important factor. This was seen in the differential effects that occurred after exposure to pulsed vs continuous-wave RFR, plane vs circularly polarized waves, and the pattern of energy absorption in the body of the animal. These data raised the question whether the whole body SAR could be used as the sole factor in considering the biological effects of RFR. Other exposure factors also should be considered.

A series of experiments were carried out to investigate the neural mechanisms mediating the effects of low-level RFR on the cholinergic systems of the rat brain. Our experiments [Lai et al., 1987b, 1989b] showed that some of the neurological effects of RFR are mediated by endogenous opioids in the brain. Since there are three types of endogenous opioid receptors, μ, δ, and κ, in the brain [Mansour et al., 1987; Katoh et al., 1990], the types of opioid receptors mediating the effects of RFR were studied in a further experiment [Lai et al., 1992b]. We found that RFR-induced decrease in HACU in the hippocampus could be blocked by injection of specific μ, δ, and κ opioid-antagonists into the lateral cerebroventricle of rats before exposure to RFR (2450 MHz, 45 min at an average whole body SAR of 0.6 W/kg). Supporting the previous finding that the RFR-induced decrease in HACU in the frontal cortex was not mediated by endogenous opioids [Lai et al., 1987b], all types of opioid

receptor antagonists tested were not effective in blocking the effect in the frontal cortex.

More recent research showed that the effects of RFR on both frontal cortical and hippocampal cholinergic systems could be blocked by pretreatment with an intracerebroventricular injection of the corticotropin-releasing factor (CRF) antagonist α–helical-CRF9-41 [Lai et al., 1990]. Corticotropin-releasing factor is a hormone that has been implicated in mediating stress responses in animals [Fisher, 1989]. From the above results and data from our other research [Lai and Carino, 1990a], the following sequence of events in the brain was proposed [Lai, 1992] to be triggered by RFR:



Radiofrequency radiation (2450-MHz, 45 min exposure at an average whole body SAR of 0.6 W/kg) activates CRF, which in turn caused a decrease in the activity of the cholinergic innervations in the frontal cortex and hippocampus of the rat. In addition, the effect of CRF on the hippocampal cholinergic system was mediated by endogenous opioids via μ, δ, and κ receptors. Since these effects can be blocked by direct injection of antagonists into the ventricle of the brain, the neural mechanisms involved are located inside the central nervous system.

A series of experiments were performed to study the effects of RFR on benzodiazepine receptors in the brain. Benzodiazepine receptors have been suggested to be involved in anxiety and stress responses in animals [Polc, 1988] and have been shown to change after acute or repeated exposure to various stressors [Braestrup et al., 1979; Medina et al., 1983a, b]. Exposure to RFR has been previously shown to affect the behavioral actions of benzodiazepines [Johnson et al., 1980; Thomas et al., 1979]. 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) [Lai et al.,1992a].

Metabolism of Neural Tissues

With the changes in neurotransmitter functions after exposure to RFR, it would not be surprising to observe changes in second messenger activity in neural tissues that mediate the the reaction between a neurotransmitter and its receptors on the cell membrane. Studies in this area are sparse. Gandhi and Ross [1989] 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, thereby suggesting an increase in inositol metabolism. These phospholipids play an important role in membrane functions and act as second messengers in the transmission of neural information between neurons.

Several studies have investigated the effects of RFR exposure on energy metabolism in the rat brain. 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.

Sanders et al. [1980] 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). Decreases in ATP and CP and an increase in NADH (the reduced form of NAD) concentration were observed in the cerebral cortex. These changes were found at both power densities of exposure. Furthermore, the authors 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.

In another study [Sanders and Joines, 1984] the effects of hyperthermia and hyperthermia plus RFR were studied. The authors reported brain temperature-dependent decreases in ATP and CP concentrations in the brain. Radiofrequency radiation (591 MHz, continuous-wave, at 13.8 mW/cm^2, for 0.5-5 min) caused a further decline in the concentration of the compounds in addition to the temperature effect.

Sanders et al. [1984] 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 their paper, Sanders et al. [1984] made an interesting deduction. Under normal conditions, the concentration of ATP in a cell is maintained by conversion of CP into ATP by the enzyme creatine phosphate kinase. Thus, the concentration of ATP is generally more stable than that of CP, and the concentration of ATP does not decline unless the CP concentration has reached 60% of normal. In the case of the RFR, the concentration of ATP dropped as fast as the CP level. Thus, they speculated that the radiation may have inhibited creatine phosphate kinase activity in the brain tissue.

In a further study [Sanders et al., 1985], the effects of continuous-wave, sinusoidally amplitude-modulated, and pulsed 591-MHz RFR were compared after five min 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 the modulation frequency. 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 experiment related to brain metabolism after RFR exposure was performed by Wilson et al. [1980]. They studied the uptake of ^{14}C-2-deoxy-D-glucose (2-DG) in the auditory system of the rat after exposure to either pulsed 2450 MHz (20 μs pulses, 10 pps, average power density 2.5 mW/cm^2) or continuous-wave 918-MHz (2.5-10 mW/cm^2) RFR for 45 min. One middle ear of the rats was destroyed before the experiment. Neurons that have increased activity (metabolism) will pick up an increased amount of 2-DG, which will accumulate in the cell body, since it is not a normal substrate for cellular functions. Location in the brain of these neurons can then be identified histologically by the autoradiographic technique. The authors reported a symmetrical (in both brain hemispheres) increase in 2-DG

uptake in the inferior colliculus, medial geniculate nucleus, and various other nuclei in the auditory system after exposure. Asymmetric (contralateral to the intact middle ear) uptake was seen in the auditory system of rats exposed to auditory stimuli. Further experiment showed that unilateral destruction of the cochlea before the experiment produced asymmetric 2-DG uptake in the brain after exposure to the RFR. These data confirmed the findings of Chou et al. [1975] and Chou and Galambos [1979] that the cochlea and not the middle ear contributes to the auditory perception of pulsed RFR. However, it is surprising that both continuous-wave and pulsed RFRs produced similar patterns of 2-DG uptake in the auditory system and only pulsed RFR elicited auditory sensation.

Calcium Efflux

Another important topic of research on the neurochemical effects of electromagnetic radiation 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.

Bawin et al. [1975] 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. Bicarbonate and pH of the medium were found to be important factors in the effect [Bawin et al., 1978].

In vitro increase in calcium efflux from the chick brain was further confirmed by Blackman et al. [1979, 1985, 1980a,b] using amplitude-modulated 147-MHz and 50-MHz RFR. They also reported both modulation-frequency windows and power windows in the effect. 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. [1979] 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.

Two other papers reported no significant change in calcium efflux from the rat brain irradiated with RFR. Shelton and Merritt [1981] exposed rat brains to 1000-MHz RFR pulse-modulated with square waves (16 and 32 Hz, power density 0.5-15 mW/cm^2). They observed no change in calcium efflux from the tissue. Merritt et al. [1982] exposed rat brains with either 1000-MHz pulsed radiation modulated at 16 Hz at 1 or 10 mW/cm^2 (SARs 0.29 and 2.9 W/kg), or to a pulse-modulated 2450-MHz RFR at 1 mW/cm^2 (SAR 0.3 W/kg). No significant change in calcium efflux was observed in this experiment. These researchers also exposed animals, in vivo, injected with radioactive calcium to pulsed 2060-MHz RFR at different combinations of intensities and pulse repetition rates. No significant change in radioactive calcium content was found in the brains of the animals after 20 min of exposure. It is not known whether the discrepancies between these data and the findings of Bawin et al. [1975, 1978] and Blackman et al. [1979] were due to the use of square-wave instead of sinusoidally modulated radiation or due to the different species of animals studied. Electromagnetic field-induced increases in calcium efflux have also been reported in tissues obtained from different species of animals. Adey et al. [1982] 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 [1982] 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. More recently, Dutta et al. [1984] 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 [Dutta et al., 1989] 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, the authors 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 more recent studies, Blackman explored the effects of different exposure conditions [Blackman et al., 1988, 1989, 1991]. 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. The temperature in which the experiment was run was also reported to be an important factor of the efflux effect. A hypothetical model involving the dynamic properties of cell membrane has been proposed to account for these effects [Blackman et al., 1989].

In addition to calcium ion, changes in other trace metal ions in the central nervous system have also been reported after RFR exposure. Stavinoha et al. [1976] reported an increase in zinc concentration in the cerebral cortex of rats exposed to 19-MHz RFR. Increases in the concentration of iron in the cerebral cortex, hippocampus, striatum, hypothalamus, midbrain, medulla, and cerebellum; manganese in the cerebral cortex and medulla; and copper in the cerebral cortex were reported in the rat after 10 min of exposure to 1600-MHz RFR at 80 mW/cm^2 (SAR 48 W/kg) [Chamness et al., 1976]. The significance of these changes is not known. The effects could be as a result of hyperthermia, because the colonic temperature of the animals increased by as much as 4.5 ^oC after exposure.

RADIOFREQUENCY RADIATION AND THE ACTIONS OF PSYCHOACTIVE DRUGS

The actions of psychoactive drugs depend on the functions of the neurotransmitter systems in the brain. Changes in neurotransmitter functions after RFR exposure will inevitably lead to changes in the actions of psychoactive drugs administered to the animal. On the other hand, if there is no change in the pharmacokinetics of drugs after RFR exposure, observed changes in psychoactive drug actions would imply RFR-induced changes in neurotransmitter functions in the animal. Pharmacological studies of RFR effects provide an important insight into the neural mechanisms affected by exposure to RFR.

Psychoactive drugs of various types have been tested in animals after exposure to RFR. Since an effect of RFR is to increase the body temperature of an animal, special attention has been given to study the effects of psychoactive drugs on the thermal effect of RFR. Jauchem [1985] has reviewed the effects of drugs on thermal responses to RFR. Radiofrequency radiation of high power densities was used in these studies.

Some psychoactive drugs have a profound effect on thermoregulation and, thus, alter the body temperature of an animal upon administration. The effect could be due to direct drug action on the thermoregulatory mechanism within the central nervous system or effects on autonomic functions such as respiration, cardiovascular and muscular systems, which lead to changes in body temperature. Several studies have investigated the neuroleptic (antipsychotic) drug, chlorpromazine. Michaelson et al. [1961] reported that chlorpromazine

enhanced the thermal effect of RFR in dogs (2800 MHz, pulsed, 165 mW/cm^2). Drug-treated animals had a faster rate of body temperature increase and a higher peak temperature when irradiated with RFR. Similar effects were seen with pentobarbital and morphine sulfate. On the other hand, Jauchem et al. [1983, 1985] reported that chlorpromazine attenuated the thermal effect of RFR in ketamine anesthetized rats. The drug slowed the rate of rise in colonic temperature (from 38.5-39.5 ^{o}C) and facilitated the return to base line temperature after exposure to RFR (2800-MHz, 14 W/kg); however, when the body temperature was allowed to rise to a lethal level, chlorpromazine potentiated the effect of RFR. Interestingly, haloperidol, another neuroleptic drug, was found to have no significant effect on RFR-induced change in colonic temperature. In another study [Lobanova, 1974b], the hyperthermic effect of RFR (40 mW/cm^2) was found to be attenuated by pretreatment with chlorpromazine or acetylcholine and enhanced by epinephrine and atropine (a cholinergic antagonist). This suggests a role of acetylcholine in modifying RFR-induced hyperthermia. Indeed, Ashani et al. [1980] reported that acute RFR exposure (10 min at 10 mW/cm^2) enhanced the hypothermic effects of AChE inhibitors. On the other hand, Jauchem et al. [1983, 1984] observed no significant effect of atropine and propranolol (an adrenergic antagonist) on the hyperthermia produced in ketamine anesthesized rats exposed to 2800-MHz RFR (SAR 14 W/kg).

Several studies investigated the effects of RFR on the actions of barbituates. Barbituates are sedative-hypnotic compounds, which produce narcosis (sleep states and loss of consciousness), synchronization of EEG, and poikilothermia (i.e., loss of body temperature regulatory functions). Baranski and Edelwejn [1974] reported that acute exposure to pulsed RFR (20 mW/cm^2) had little effect on the EEG pattern of rabbits given phenobarbital; however, after 200 h of exposure (at 7 mW/cm^2), desynchronization rather than synchronization of the EEG pattern was seen after phenobarbital administration. Rabbits anesthetized with pentobarbital and subjected to 5 min of RFR (0.7-2.8 mW/cm^2) showed periods of alternating EEG arousal (desynchronization) and sedation (synchronization) and periods of behavioral arousal. The duration of EEG arousal seemed to correlate with the power density of RFR [Goldstein and Sisko, 1974].

Wangemann and Cleary [1976] reported that short term RFR exposure (5-50 mW/cm^2) decreased the duration of pentobarbital induced loss of righting reflex in the rabbit. The investigators speculated that the effect was due to the thermal effect of RFR, which decreased the concentration of pentobarbital in the central nervous system. Supporting this, Bruce-Wolfe and Justesen [1985] reported that warming an animal with RFR while under anesthesia could attenuate the effects of pentobarbital. Mice exposed to continuous-wave 2450-MHz RFR at 25 and 50 mW/cm^2 also showed a power density-dependent reduction in the duration of hexobarbital-induced anesthesia [Blackwell, 1980]. On the other hand, Benson et al. [1983] reported decreased onset-time and prolonged duration of phenobarbital-induced narcosis in mice after exposure to RFR (10 mW/cm^2, 10 min). They showed that the effect was caused by an increase in deposition of phenobarbital in the brain. We [Lai et al., 1984a] have shown that after 45 min of exposure to pulsed 2450-MHz RFR (2 μs pulses, 500 pps, whole-body average SAR 0.6 W/kg), the pentobarbital-induced narcosis and hypothermia in the rat were enhanced. We also found that exposure of rats in two different orientations (with the head of the rat facing or away from the source of the RFR) had different effects on the pentobarbital-induced hypothermia, even though the average whole body SAR was similar under the two conditions. These data suggest that the pattern of localized SAR in the body of the animal might be an important determinant of the outcome of the effect.

When the body temperature of an animal is raised above a certain level, convulsions result. Various psychoactive drugs were studied in an attempt to alter the convulsive effect of RFR. Studies have also been carried out to investigate whether RFR exposure altered the potency of convulsants. It was reported that the susceptibility of rats to the convulsive effect of RFR (14 mW/cm^2, 2 h) was decreased by chloral hydrate, sodium pentobarbital, and

bemegride, and enhanced by chlorpromazine, epinephrine, atropine, acetylcholine, nicotine, and monoamine oxidase inhibitors, but was not significantly affected by serotonin [Lobanova, 1974a]. Some of these results can be explained by the pharmacological properties of the drug tested. Pentobarbital and chloral hydrate are hypnotic agents and are known to have anticonvulsant effects. Chlorpromazine, nicotine, and monoamine oxidase inhibitors can lower the seizure threshold or induce convulsions depending on their dosages. Atropine, a cholinergic antagonist, has been shown to enhance the seizure threshold. It is puzzling that bemegride decreased RFR induced seizures, since it is a nervous system stimulant with similar pharmacological actions as the convulsant pentylenetetrazol.

Exposure to pulsed RFR (7 and 20 mW/cm^2) was reported to affect the effects of the convulsants, pentylenetetrazol and strychnine, on EEG activity [Baranski and Edelwejn, 1974]. Another study showed that low-level RFR altered the sensitivity of animals to the seizure inducing effect of pentylenetetrazol [Servantie et al., 1974]. Rats and mice were subjected to 8-36 days of pulsed RFR (3000 MHz, 0.9-1.2 μs pulses, 525 pps, 5 mW/cm^2). No significant change in susceptibility to the drug was seen after eight days of exposure; however, a decrease in susceptibility was observed after 15 days, and an increase in susceptibility was observed after 20, 27, and 36 days of irradiation. Mice became more susceptible to the convulsive effect of pentylenetetrazol and more animals died from convulsions. Thus, the sensitivity of the nervous system to the convulsive action of the drug changed as a function of the duration of exposure. In another study, Pappas et al. [1983] showed in the rat that acute (30 min) exposure to 2700-MHz pulsed RFR at 5, 10, 15, and 20 mW/cm^2 (SARs 0.75, 1.5, 2.25, and 3.0 W/kg, respectively) produced no significant interaction effect on pentylenetetrazol induced seizure or the efficacy of chlordiazepoxide (an anticonvulsant) to block the seizure.

Drugs affecting cholinergic functions in the nervous system have also been studied. Chronic RFR-exposed rats (10-15 days) were found to be less susceptible to the paralytic effect of curare-like drugs, which block nicotinic cholinergic transmission. A similar effect was observed on muscle preparations from the irradiated rats. Presumably, the cholinergic transmission in the neuromuscular junction was affected by RFR. Ashani et al. [1980] reported that acute pulsed RFR (10 min, 10 mW/cm^2) enhanced the hypothermic effects of an inhibitor of AChE (the degradation enzyme of acetylcholine). The site of this effect was determined to be located inside the central nervous system. Monahan [1988] also reported that RFR (2450 MHz, continuous-wave, whole body SARs 0.5-2.0 W/kg) affected the actions of scopolamine, a cholinergic antagonist, and physostigmine, a cholinergic agonist, on motor activity of mice in a maze. The data suggested enhancement of cholinergic activity after RFR irradiation.

Several studies investigated the actions of benzodiazepines, a group of drugs used for anticonvulsion, sedation-hypnosis, and antianxiety purposes. Two of the most commonly used benzodiazepines for the treatment of anxiety disorders are chlordiazepoxide (Librium) and diazepam (Valium). Low-level pulsed RFR (1 mW/cm^2, whole body SAR 0.2 W/kg) potentiated the effect of chlordiazepoxide on bar-pressing behavior of rats working on a DRL-schedule for food reinforcement; however, the same authors also reported no interaction effects between RFR and diazepam on bar pressing [Thomas et al., 1979, 1980].

Increase in brain benzodiazepine receptors in the brain after RFR exposure [Lai et al, 1992a] could explain the former effect. A possible explanation for the discrepancy of the results observed with chlordiazepoxide and diazepam was that diazepam has a higher potency than chlordiazepoxide. The potency of diazepam that was effective in attenuation of experimental conflict, an animal model of anxiety, was about four times that of chlordiazepoxide [Lippa et al., 1978], and the in vitro relative affinity of diazepam with benzodiazepine receptors was 30-65 times that of chlordiazepoxide [Braestrup and Squires, 1978; Mohler and Okada, 1977]. The ranges of diazepam and chlordiazepoxide used in the Thomas studies [Thomas et al., 1979, 1980] were 0.5-20 and 1-40 mg/kg, respectively. Thus, the doses of

diazepam studied might be equivalent or higher in potency than the highest dose of chlordiazepoxide used. This supposition was supported by the observation in the Thomas studies that the effects of the two drugs were different. The dose-response curve of chlordiazepoxide on the DRL-schedule operant responses showed a dose-dependent inverted-U function, i.e., potentiation at medium dose, attenuation at higher dose, and only the portion of the response-curve that showed potentiation was affected by RFR [Thomas et al., 1979]. In the study of Thomas et al. [1980] on diazepam, only attenuation of DRL-responses was observed. Thus, the dose range of diazepam used in the study was at the attenuation portion of the dose-response function, which is not affected by RFR. These dose-dependent potentiation and attenuation effects of benzodiazepines on the operant response may involve different neural mechanisms. Radiofrequency radiation may only affect and enhance the potentiating and not the attenuating effect of benzodiazepines, which is possible because our research [Lai et al., 1992a] showed that the effect of RFR on benzodiazepine receptors is brain-region selective. Thus, the data of Thomas et al. [1979, 1980] on the interaction of RFR irradiation on benzodiazepine actions could be explained by a selective increase in benzodiazepine receptors in different regions of the brain. Another possibility is that RFR affects only the subtype of benzodiazepine receptors related to antianxiety effect and not another subtype related to the sedative-hypnotic action of the drugs. In the dose-response curve of benzodiazepine on DRL-schedule maintained behavior, the potentiation portion may be due to the former receptor subtypes and the attenuation portion the latter subtype. There is ample evidence suggesting that different subtypes of benzodiazepine receptors subserve antianxiety and sedative effects [Polc, 1988].

In addition to the above studies on the effect of RFR on benzodiazepines, Monahan and Henton [1979] trained mice to avoid or escape from 2450-MHz RFR (45 W/kg) under an avoidance paradigm. They reported that pretreatment of the animals with chlordiazepoxide decreased the avoidance response and increased the escape responses, which led to an increase in the animal's cumulative exposure to RFR after the drug treatment. The authors speculated that RFR potentiated the effect of chlordiazepoxide and caused a decrement in the avoidance response. It is also interesting that in the procedure the presence of RFR was signalled simultaneously with a tone and the animal could elicit an avoidance response, which resets the timer and delays the further presentation of RFR. Thus, the procedure had both signalled and continuous avoidance components. However, the data indicate that the effect was more like a continuous avoidance paradigm. Generally, anxiolyltic agents like benzodiazepines decrease both avoidance and escape behavior in a signalled-avoidance paradigm, but they can selectively decrease the avoidance response and leave the escape responding intact under a continuous avoidance paradigm.

Johnson et al. [1980] reported that repeated exposure (twenty-one 45-min sessions) to RFR (2450 MHz, pulsed, average whole body SAR 0.6 W/kg) reduced the sedative hypnotic effect, but increased the feeding behavior induced by diazepam. Hjeresen et al. [1987] reported that the attenuation effect of a single (45 min) RFR exposure (2450 MHz, CW, average whole body SAR 0.3 W/kg) on ethanol-induced hypothermia was blocked by treating the rat with the benzodiazepine antagonist, RO 15-1778. The data indicated that benzodiazepine receptors in the brain might mediate the effects of RFR on ethanol-hypothermia. In a more recent study, Quock et al. [1990] investigated the influence of RFR exposure on the effect of chlordiazepoxide on the stair-case test for mouse, a test for both the sedative and antianxiety effects of benzodiazepines. They reported that acute exposure (5 min at a whole body average SAR of 36 W/kg) caused a significant reduction of the sedative, but not the antianxiety effect of chlordiazepoxide. The effect was probably related to hyperthermia. Some of the above effects of RFR on benzodiazepine actions can be explained by our finding [Lai et al., 1992a] that acute RFR exposure increased benzodiazepine receptors in selective regions of the brain and that adaptation occurred after repeated exposure.

On the other hand, central benzodiazepine receptors can also affect seizure susceptibility in animals. Benzodiazepines are widely used as anticonvulsants. Exposure to RFR has been shown to affect seizure and convulsion susceptibility in animals. For example, Stverak et al. [1974] reported that chronic exposure to pulsed RFR attenuated audiogenic seizures in seizure-sensitive rats. Servantie et al. [1974] showed that mice chronically exposed to pulsed RFR initially showed a decrease and then an increase in susceptibility to the convulsant pentylenetetrazol. However, Pappas et al. [1983] showed no significant interaction effect of RFR on pentylenetetrazol-induced seizures nor the efficacy of chlordiazepoxide to block the seizure in rats. A more thorough study of the different parameters of RFR exposure on benzodiazepine receptors in the brain may explain these findings. Benzodiazepine receptors are very dynamic and can undergo rapid changes in properties in response to environmental stimuli [Braestrup et al., 1979; Lai and Carino, 1990b; Medina et al., 1983a,b; Soubrie et al., 1980; Weizman et al., 1989]. However, the direction of change and extent of effect depend on the stimulus and experimental conditions.

We conducted experiments to study the effect of acute RFR exposure on the actions of various psychoactive drugs [Lai et al., 1983; 1984a,b]. We found that acute (45 min) exposure to pulsed 2450-MHz RFR (2 μs pulses, 500 pps, 1 mW/cm^2, whole body average SAR 0.6 W/kg) enhanced apomorphine-hypothermia and stereotypy, morphine-catalepsy, and pentobarbital-hypothermia and narcosis, but it attenuated amphetamine-hyperthermia and ethanol-hypothermia. These psychoactive drugs are lipid-soluble and readily enter the central nervous system and the effects observed are not unidirectional, i.e., depending on the drug studied, increase or decrease in action was observed after RFR exposure. Therefore, these effects cannot be explained as a change in entry of the drugs into the brain, e.g., change in blood-brain barrier permeability or alteration in drug metabolism as a result of RFR exposure. Our finding that acute low-level RFR attenuated ethanol-hypothermia in the rat was replicated by Hjeresen et al. [1988] at a lower whole body average SAR of 0.3 W/kg. Blood ethanol level measurements indicated that the effect was not due to changes in metabolism or disposition of ethanol in the body. Results from further experiments [Hjeresen et al., 1989] suggested that the β-adrenergic mechanism in the brain might be involved in the attenuation effect of RFR on ethanol-induced hypothermia in the rat.

We further found that the effects of RFR on amphetamine-hyperthermia [Lai et al., 1986b] and ethanol-hypothermia could be classically conditioned to cues in the exposure environment after repeated exposure. Another interesting finding in our research was that some of the effects of RFR on the actions of the psychoactive drugs could be blocked by pretreating the rats with narcotic antagonists before exposure, suggesting the involvement of endogenous opioids [Lai et al., 1986b]. The hypothesis that low-level RFR activates endogenous opioids in the brain was further supported by an experiment showing that the withdrawal syndromes in morphine-dependent rats could be attenuated by RFR exposure [Lai et al., 1986a]. This hypothesis can explain most of the RFR-psychoactive drug interaction effects reported in our studies [see Table I in Lai et al., 1987a].

In another study [Lai et al., 1984b], water-deprived rats were allowed to drink a 10% sucrose solution from a bottle in the waveguide. Exposure to pulsed 2450-MHz RFR (2 μs pulses, 500 pps, 1 mW/cm^2, SAR 0.6 W/kg) did not significantly affect the consumption of the sucrose solution. However, when the sucrose solution was substituted by a 10% sucrose-15% ethanol solution, the rats drank ~25% more when they were exposed to the RFR than when they were sham exposed. The hypothesis that RFR activates endogenous opioids in the brain can also explain the increased ethanol consumption during RFR exposure. Recent studies have shown that activation of opioid mechanisms in the central nervous system can induce voluntary ethanol drinking in the rat [Nichols et al., 1991; Reid et al., 1991; Wild and Reid, 1990].

Frey and Wesler [1983] studied the effect of low-level RFR (1200 MHz, pulsed, 0.2

mW/cm^2, 15 min) on central dopaminergic functions. Radiofrequency radiation was found to attenuate the effect to both a high dose (1 mg/kg, IP) and a low dose (0.1 mg/kg, IP) of apomorphine on the latency of the tail-flick responses in the rat. The tail-flick test is a measure of pain perception in animals. These data are difficult to explain, since high dose and low dose of apomorphine affect predominantly the post- and presynaptic-dopamine receptors, respectively. These two types of dopamine receptors have opposite effects on dopamine transmission and functions. Other experiments indicating an effect of RFR on dopamine function in the brain are those of Michaelson et al. [1961] and Jauchem et al. [1983, 1985] showing the effect of chlorpromazine on RFR-induced hyperthermia, and our experiment showing an enhancement of apomorphine-hypothermia by RFR [Lai et al., 1983]. Chlorpromazine and apomorphine are dopamine antagonist and agonist, respectively. On the other hand, Thomas et al. [1980] reported no significant interaction effect between chlorpromazine and pulsed RFR (2800 MHz, 2 μs pulses, 500 pps, 1 mW/cm^2, SAR 0.2 W/kg) on rats responding on a fixed interval reinforcement schedule for food reward. However, Thomas and Maitland [1979] reported that exposure to pulsed 2450-MHz RFR (2 μs pulses, 500 pps, 1 mW/cm^2, SAR 0.2 W/kg) potentiated the effect of d-amphetamine on rats responding on a DRL-schedule of reinforcement. Amphetamine is an agonist of both dopamine and norepinephrine functions in the brain.

Two studies imply RFR affects serotonergic activity in the brain. Galloway and Waxler [1977] reported interaction between RFR and a serotonergic drug. Rhesus monkeys trained on a color-matching task were irradiated with continuous-wave 2450-MHz RFR at different dose rates. The animals were also treated with the serotonergic drug fenfluramine, which inhibits granule reuptake and storage of serotonin in nerve terminals and causes a long-lasting depletion of serotonin in the brain. Radiofrequency radiation alone had no significant effect on performance, whereas fenfluramine alone decreased the response accuracy and response rate in performing the task. Exposure to RFR plus the drug treatment produced a synergistic effect. A severe disruption of responding was observed. The authors speculated that RFR may act like fenfluramine, i.e., decreases serotonergic functions in the brain. This may be related to the finding of Frey [1977] who reported that RFR exposure decreased tail pinch-induced aggressive behavior in the rat. Fenfluramine and other drug treatments that decrease serotonergic functions in the brain were shown to suppress aggressive behavior elicited by electric foot-shock in rats [Panksepp et al., 1973].

Results from one of our experiments also indicated an increase in serotonergic activity in the brain of rats exposed to RFR. We [Lai et al., 1984c] observed an increase in body temperature (~1.0 ^{o}C) in the rat after acute (45 min) exposure to pulsed 2450-MHz RFR (2 μs pulses, 500 pps, 1 mW/cm^2, SAR 0.6 W/kg). This hyperthermic effect was blocked by pretreating the rats before exposure with the serotonin antagonists, cinanserin, cyproheptadine, and metergoline, but not by the peripheral serotonin antagonist, xylamidine, implying that the effect is mediated by serotonergic mechanism inside the central nervous system.

The findings that RFR can affect (potentiate or attenuate) the actions of psychoactive drugs could have important implication in considering the possible hazardous effects of the radiation. Most of the drugs studied, such as the benzodiazepines and neuroleptics, are widely used for therapeutic purposes. On the other hand, drugs can enhance the biological effects of RFR. Example are the studies of Kues and Monahan [1992] and Kues et al. [1990; 1992] showing synergistic effects of drugs on corneal endothelium damages and retinal degeneration in the monkey induced by repeated exposure to RFR. They found that application of the drugs timolol and pilocarpine to the eye before RFR exposure could lower the threshold of the RFR effect by 10 folds (from 10 to 1 mW/cm^2). Timolol and pilocarpine are commonly used in the treatment of glaucoma.

PSYCHOLOGICAL EFFECTS OF RADIOFREQUENCY RADIATION

A necessary consequence of change in neurological activity is a change in behavior. If RFR alters electrophysiological and neurochemical functions of the nervous system, changes in behavior will result. Effects of RFR on both spontaneous and learned behaviors have been investigated.

Spontaneous Behaviors

The effects of RFR on motor activity were the subjects of various studies. Changes in motor activity are generally regarded as indications of changes in the arousal state of an animal. Hunt et al. [1975] reported increased motor activity in rats after 30 min of exposure to 2450-MHz RFR (SAR of 6.3 W/kg) and decreased swimming speed in cold (24 ^{o}C) water. However, Roberti [1975] reported no significant change in locomotor activity in rats after long term (185-408 h) exposure to RFR at different frequencies and intensities (SARs 0.15-83 W/kg). Modak et al. [1981] reported a decrease in motor activity in rats exposed to a single pulse (15 or 25 ms) of 2450-MHz RFR, which increased the brain temperature by 2-4 ^{o}C.

Mitchell et al. [1977] reported an increase in motor activity on a small platform of rats exposed to 2450-MHz RFR (average SAR 2.3 W/kg, 5 hr/day, 5 days/week for 22 weeks). Motor activity of the RFR exposed rats increased during the first week of exposure and stayed higher than controls throughout the period of the experiment. Moe et al. [1976] reported a decrease in motor activity of rats exposed to RFR (918 MHz, SARs 3.6-4.2 W/kg) during the dark period of the light-dark cycle in a chronic exposure experiment (10 h/night for 3 weeks). Lovely et al. [1977] repeated the experiment using a lower intensity (2.5 mW/cm^2, SARs 0.9-1.0 W/kg, 10 h/night, 13 weeks) and found no significant change in motor activity in the exposed rats. Frey [1977] subjected rats to 1300-MHz pulsed RFR (0.5 ms pulses, 1000 pps, average power density of 0.65 or 0.2 mW/cm^2, peak power densities 1.3 and 0.4 mW/cm^2). He reported a decrease in tail pinch-induced aggressive behavior in RFR-exposed rats. Increased latency, decrease in duration, and episodes of fighting after tail pinching were observed between two rats being irradiated with RFR. Decrease in motor coordination on a motor-rod was also reported in pulsed RFR-exposed (1300 and 1500 MHz, 0.5 ms pulses, 1000 pps) rats. The effect occurred at peak power densities between 0.4 and 2.8 mW/cm^2.

Rudnev et al. [1978] studied the behavior of rats exposed to 2375-MHz RFR at 0.5 mW/cm^2 (SAR 0.1 W/kg), 7 h/day for 1 month. They reported decreases in food intake, balancing time in a treadmill and inclined rod, and motor activity in an open-field after 20 days of exposure. Interestingly, the open-field activity was found to be increased even at 3 months postexposure. In a long-term exposure study [Johnson et al., 1983], rats were exposed to pulsed 2450-MHz RFR (10 μs pulses, 800 pps) from 8 weeks to 25 months of age (22 h/day). The average whole body SAR varied as the weight of the rats increased and was between 0.4-0.15 W/kg. Open field activity was measured in 3-min sessions with an electronic open-field apparatus once every 6 weeks during the first 15 months and at 12 week intervals in the final 10 weeks of exposure. They reported a significantly lower open field activity only at the first test session and a rise in the blood corticosterone level was also observed at that time. The authors speculated that RFR might be minimally stressful to the rats.

D'Andrea et al. [1979, 1980] reported decreased motor activity on a stabilimetric platform and no significant change in running wheel activity measured overnight in rats exposed to 2450-MHz RFR (5 mW/cm^2, SAR 1.2 W/kg). However, an increase in both

measurements was observed in rats exposed to 915-MHz RFR (5 mW/cm^2, SAR 2.5 W/kg). These changes in locomotor activity could be due to the thermal effect of RFR.

In a more recent experiment, Mitchell et al. [1988] studied several behavioral responses in rats after 7 h of exposure to continuous-wave 2450-MHz RFR (10 mW/cm^2, average SAR 2.7 W/kg). Decreases in motor activity and responsiveness (startle) to loud noise (8 kHz, 100 dB) were observed immediately after exposure. The rats were then trained to perform a passive avoidance task and tested for retention of the learning one week later. There was no significant difference in retention between the RFR-exposed and sham-exposed animals. The authors concluded that RFR altered responsiveness to novel environmental stimuli in the rat.

Two studies investigated the effects of pre- and postnatal-RFR on behavior. Kaplan et al. [1982] exposed groups of pregnant squirrel monkeys starting at the second trimester of pregnancy to 2450-MHz RFR at SARs of 0, 0.034, 0.34, and 3.4 W/kg (3 h/day, 5 days/week). The motor activity of the monkeys was observed at different times during the third trimester. No significant difference was observed among the different exposure groups. After birth, some dams and neonates were exposed for 6 months at the same prenatal conditions and then the offspring were exposed for another 6 months. Behavior of the mothers and offspring was observed and scored each week for the first 24 weeks postpartum. The authors observed no significant difference in maternal behavior or the general activity of the offspring among the different exposure groups. Visual-evoked EEG changes in the occipital region of the skull of the offspring were also studied at 6, 9, and 12 months of age. No significant effect of perinatal RFR-exposure was reported.

In another study [Galvin et al., 1986], rats were exposed to 2450-MHz RFR (10 mW/cm^2, 3 h/day) either prenatally (days 5-20 of gestation, whole body SAR estimated to be 2-4 W/kg) or perinatally (prenatally and on days 2-20 postnatally, whole body SARs 16.5-5.5 W/kg). Several behaviors including motor behavior, startle to acoustic and air-puff stimuli, fore- and hind-limb grip strength, negative geotaxis, reaction to thermal stimulation, and swimming endurance were studied in the rats at various times postnatally. They reported a decrease in swimming endurance (time remaining afloat in 20 ^{o}C water with a weight clipped to the tail) in 30-day old perinatally-exposed rats. The air-puff startle response was enhanced in magnitude in the prenatally exposed rats at 30 days, but decreased at 100 days of age. The authors concluded that perinatal exposure to RFR altered the endurance and gross motor activity in the rat. It would be interesting to study the neurochemistry or brain morphology of these animals. As described in a previous section, Albert et al. [1981a,b] and Albert and Sherif [1988] observed morphological changes in the cerebellum of rats subjected to RFR exposure perinatally at lower SAR (2-3 W/kg). It is well known that interference of cerebellar maturation can affect an animal's motor development [Altman, 1975].

O'Connor [1988] exposed pregnant rats to continuous-wave 2450-MHz (27-30 mW/cm^2) RFR between day 1 to day 18 or 19 of gestation (6 h/day). Their offspring were studied at different ages. She reported no significant effect of prenatal RFR exposure on visual cliff test, open field behavior, climbing behavior on an inclined plane, and avoidance behavior in a shuttlebox. The exposed animals showed altered sensitivity to thermally related tests evidenced by preference for the cooler section of a temperature-gradient alley way, longer latency to develop thermally induced seizure, and formed smaller huddle groups at 5 days of age.

Learned Bahaviors

Many studies have investigated the effect of RFR exposure on learned behavior. King et al. [1971] used RFR as the cue in a conditioned suppression experiment. In conditioned suppression an animal is first trained to elicit a certain response (e.g., bar-press for food). Once a steady rate of response is attained, a stimulus (e.g., a tone) will signify the on-coming of a negative reinforcement (e.g., electric foot shock). The animal will soon learn the

significance of the stimulus and a decrease in responding (conditioned suppression) will occur after the presentation of the stimulus. In the experiment of King et al. [1971], rats were trained to respond at a fixed-ratio schedule for sugar water reward. In a 2-h session, either a tone or RFR would be presented and occasionally followed by an electric foot shock. Radiofrequency radiation of 2450 MHz, modulated at 12 and 60 Hz and at SARs of 0.6, 1.2, 2.4, 4.8, and 6.4 W/kg were used as the conditioned stimulus. With training, consistent conditioned suppression was observed with RFR at 2.4 W/kg and higher.

Several studies used RFR as a noxious stimulus, i.e., a negative reinforcer, to induce or maintain conditioned behavior. In an earlier paper, Monahan and Ho [1976] speculated that mice exposed to RFR tended to change their body orientation in order to reduce the SAR in the body, suggesting that they were avoiding the radiation. To support the point that RFR is a noxious stimulus, Monahan and Henton [1977b] demonstrated that mice can be trained to elicit an operant response in order to escape or avoid RFR (2450-MHz, 40 W/kg).

In a series of experiments, Frey and his associates [Frey and Feld, 1975; Frey et al., 1975] demonstrated that rats spent less time in the unshielded compartment of a shuttlebox, when the box was exposed to 1200-MHz pulsed RFR (0.5 μs pulses, 1000 pps, average power density 0.2 mW/cm^2, peak power density 2.1 mW/cm^2) than during sham exposure. When a continuous-wave RFR (1200-MHz, 2.4 mW/cm^2) was used, rats showed no significant preference to remain in the shielded or unshielded side of the box. The authors also reported that rats exposed to the pulsed RFR were more active. Hjeresen et al. [1979] replicated this finding using pulsed 2880-MHz RFR (2.3 μs pulses, 100 pps, average power density 9.5 mW/cm^2) and showed that the preference to remain in the shielded side of a shuttlebox during RFR exposure could be generalized to a 37.5-kHz tone. Masking the radiation-induced auditory effect with a 10-20 kHz noise also prevented the development of shuttlebox-side preference during pulsed RFR exposure. These data suggest that the pulsed RFR-induced side preference is due to the auditory effect. In the studies of Frey et al. [1975] and Hjeresen et al. [1979] increase in motor activity was also reported when the animals were exposed to the pulsed RFR. Interestingly, this pulsed RFR-induced increase in motor activity was not affected by noise masking. Thus, the RFR avoidance and enhancement in motor activity by pulsed RFR may involve different neural mechanisms. Related to the above experiments is that the auditory effect of pulsed RFR can be used as a cue to modify an animal's behavior. Johnson et al. [1976] trained rats to respond (making nose pokes) on a fixed ratio reinforcement schedule for food pellets in the presence of a tone (7.5 kHz, 10 pps, 3 μs pulses). Reinforced period was alternated with periods of no reward when no tone was presented. Rats, after learning this response, responded when the tone was replaced by pulsed RFR (918 MHz, 10 μs pulses, 10 pps, energy per pulse 150 μJ/cm^2) during both reinforced and unrewarded periods. Apparently, the response to the tone had generalized to the pulsed RFR.

In another experiment, Carroll et al. [1980] showed that rats did not learn to go to a 'safe' area in the exposure cage in order to avoid exposure to RFR (918-MHz, pulse modulated at 60 Hz, SAR 60 W/kg), whereas the animals learned readily to escape from electric foot shock by going to the 'safe' area. In a further study, Levinson et al. [1982] showed that rats could learn to enter a 'safe' area, when the RFR (918-MHz, 60 W/kg) was paired with a light stimulus. Entering the area would turn off both the radiation and light. They also showed that rats could learn to escape by entering the 'safe' area when RFR was presented alone, but learned at a lower rate than when the RFR was paired with the light.

Several studies investigated the effect of RFR on conditioned taste aversion. It was discovered that consumption of food or drink of novel taste followed by a treatment which produced illness, e.g., X-irradiation or poison, an animal will learn to associate the taste with the illness and will later avoid the food or drink. Different from the traditional conditioning process, where conditioning occurs only when the response is followed immediately by the reinforcement, taste aversion conditioning can occur even if the illness is induced 12 h after

the taste experience. Another characteristic of conditioned taste aversion is that the conditioning is very selective. An animal can learn to associate the taste with the illness, but not the place where the food or drink was taken, i.e., it will avoid the taste, but not the place where the food or drink was consumed. This phenomenon is known as 'belongingness', i.e., association (conditioning) between some stimulus pairs is easier than others [Garcia and Koelling, 1966; Garcia et al., 1966]. Thus, RFR has to produce the 'proper' type of adverse effect in the animal in order for conditioned taste aversion to occur.

Monahan and Henton [1977a] irradiated rats for 15 min with 915-MHz RFR of various intensities (up to a SAR of ~17 W/kg) after 15 min of access to 10% sucrose solution as a substitute for the normal drinking water. When the animals were offered the sucrose solution 24 h later, no conditioned taste aversion was observed. They drank the same amount of sucrose solution as the previous day. Conditioned taste aversion was also studied by Moe et al. [1976] and Lovely et al. [1977] in experiments of similar design in which rats were exposed chronically to 918-MHz RFR at 10 mW/cm^2 (SAR 3.9 W/kg) and 2.5 mW/cm^2 (SAR 1.0 W/kg), respectively. Rats were provided with 0.1% saccharin drinking solution during the whole period of exposure in the Moe et al. [1976] study and between the 9th to 13th week of exposure in the Lovely et al. [1977] study. They observed no significant difference in the consumption of saccharin solution, nor a preference for either water or saccharin solution between the RFR-exposed and sham-exposed animals. Thus, no taste aversion developed. Perhaps, RFR does not produce an intensive sickness or the proper type of 'belongingless' for the conditioning to occur. However, in another study, Lovely and Guy [1975] reported that rats that were exposed to continuous-wave 918-MHz RFR for 10 min at >25 mW/cm^2 (SAR ~22.5 W/kg) and then allowed to drink saccharin solution, showed a significant reduction in saccharin consumption when tested 24 h later. No significant effect was found in rats exposed to RFR at 5 or 20 mW/cm^2.

In addition to using RFR as an aversive stimulus, it has also been used as a positive reinforcer. Marr et al. [1988] reported that rhesus monkeys could be trained to press a lever on a fixed ratio schedule to obtain 2 sec-pulses of RFR (6500 MHz, 50 mW/cm^2, estimated SAR 12 W/kg) when the monkeys were placed in a cold environment (0 ^{o}C).

A study by Bermant et al. [1979] investigated the thermal effect of RFR using the classical conditioning paradigm. They reported that after repeated pairing of a 30 sec tone with RFR (2450 MHz, 10 sec at SAR 420 W/kg or 30 sec at SAR 220 W/kg), the tone when presented alone could elicit a conditioned hyperthermia from the rat. An effect which may be relevant to the finding of this experiment is that drug-induced changes in body temperature (hyperthermia or hypothermia) in animals can also be classically conditioned [Cunningham et al., 1984].

We have conducted experiments to investigate whether the effects of low-level RFR on psychoactive drug actions and central cholinergic activity can be classically conditioned to cues in the exposure environment. Classical conditioning of drug effects with environmental cues as the conditioned stimulus have been reported and such conditioned responses have been suggested to play a role in drug response, abuse, tolerance, and withdrawal [Le et al., 1979; Siegel, 1977, Siegel et al., 1982, Wikler, 1973a; Woods et al., 1969]. We found that the effects of RFR on amphetamine-induced hyperthermia and cholinergic activity in the brain can be classically conditioned to environmental cues [Lai et al., 1986b, 1987c].

In earlier experiments, we reported that acute (45 min) exposure to 2450-MHz RFR at average whole body SAR of 0.6 W/kg attenuated amphetamine-induced hyperthermia [Lai et al., 1983] and decreased HACU in the frontal cortex and hippocampus [Lai et al., 1987b] in the rat. In the conditioning experiments, rats were exposed to 2450-MHz pulsed RFR (2 μs pulses, 500 pps, 1.0 mW/cm^2, SAR 0.6 W/kg) in ten daily 45-min sessions. On day 11, animals were sham-exposed for 45 min and either amphetamine-induced hyperthermia or high-affinity choline uptake (HACU) in the frontal cortex and hippocampus was studied immediately after exposure. In this paradigm the RFR was the unconditioned stimulus and

cues in the exposure environment were the neutral stimuli, which after repeated pairing with the unconditioned stimulus became the conditioned stimulus. Thus on the 11th day when the animals were sham-exposed, the conditioned stimulus (cues in the environment) alone would elicit a conditioned response in the animals. In the case of amphetamine-induced hyperthermia [Lai et al., 1986b], we observed a potentiation of the hyperthermia in the rats after the sham exposure. Thus, the conditioned response (potentiation) was opposite to the unconditioned response (attenuation) to RFR. This is known as 'paradoxical conditioning' and is seen in many instances of classical conditioning [cf. Mackintosh, 1974]. In addition, we found in the same experiment that, similar to the unconditioned response, the conditioned response could be blocked by the drug naloxone, implying the involvement of endogenous opioids. In the case of RFR-induced changes in cholinergic activity in the brain, we [Lai et al., 1987c] found that conditioned effects also occurred in the brain of the rat after the session of sham exposure on day 11. An increase in HACU in the hippocampus (paradoxical conditioning) and a decrease in the frontal cortex were observed. In addition, we found that the effect of RFR on hippocampal HACU habituated after 10 sessions of exposure, i.e., no significant change in HACU in the hippocampus was observed in animals exposed to the RFR on day 11. On the other hand, the effect of RFR on frontal cortical HACU did not habituate after the repeated exposure.

An explanation for the paradoxical conditioning phenomenon was given by Wikler [1973b] and Eikelboom and Stewart [1982]. The direction of the conditioned response (same as or opposite to the unconditioned response) depends on the site of action of the unconditioned stimulus, whether it is on the afferent or efferent side of the affected neural feedback system. Thus, in order to further understand the neural mechanisms of the conditioned effects, the site of action of RFR on the central nervous system has to be identified.

Little work has been done to investigate the effects of RFR on memory functions. We [Lai et al., 1989b] studied the effect of acute (20 or 45 min) RFR exposure (2450-MHz, 1 mW/cm^2, SAR 0.6W/kg) on the rats' performance in a radial-arm maze, which measures spatial learning and memory functions. The maze consists of a central circular hub with arms radiating out like the spokes of a wheel. In this task, food-deprived animals are trained to explore the arms of the maze to obtain food reinforcement at the end of each arm. In each session they have to enter each arm once and a reentry is considered as an error. This task requires the so called 'working memory', i.e., the rat has to remember the arms it has already entered during the course of a session. Working memory requires the functions of the cholinergic innervations in the frontal cortex and hippocampus [Dekker et al., 1991; Levin, 1988]. Both have been shown to be affected by acute RFR exposure [Lai et al., 1987b]. We [Lai et al., 1989b] found that acute (45 min) exposure to RFR before each session of maze running significantly retarded the rats' abilities to perform in the maze. They made significantly more errors than the sham-exposed rats. This result agrees with the neurochemical finding that 45 min of RFR exposure decreased the activity of the cholinergic systems in the frontal cortex and hippocampus of the rats [Lai et al., 1987b]. However, 20 min of RFR exposure, which increased cholinergic activity in the brain, did not significantly affect maze performance. Apparently, increase in cholinergic activity cannot further improve the performance, since the neural systems involved in the memory function may be working at optimal levels under normal conditions. In a recent experiment [Lai et al., 1993], we have shown that the microwave-induced working memory deficit in the radial-arm maze was reversed by pretreating the rats before exposure with the cholinergic agonist physostigmine or the opiate antagonist naltrexone, whereas pretreatment with the peripheral opiate antagonist naloxone methiodide showed no reversal of effect. These data indicate that both cholinergic and endogenous opioid neurotransmitter sysatems inside the central nervous system are involved in the microwave-induced spatial memory deficit.

Several studies have investigated the effect of RFR on discrimination learning and responding. Hunt et al. [1975] trained rats to bar press for saccharin water rewards in the

presence (5 sec duration) of a flashing light and not to respond in the presence of a tone (unrewarded). After 30 min of exposure to 2450-MHz RFR, modulated at 20 Hz and at SAR of 6.5 or 11.0 W/kg, rats made more misses at the presence of the light, but there were no significant changes in the incidences of bar-pressing errors when the tone was on. The effect was more prominent at the higher dose rate. Galloway [1975] trained rhesus monkeys on two behavioral tasks to obtain food reward. One was a discrimination task in which the monkey had to respond appropriately depending on which of the two stimuli was presented. The other task was a repeated acquisition task in which a new sequence of responses had to be learned everyday. After training, the animals were irradiated with continuous-wave 2450-MHz RFR applied to the head prior to each subsequent behavioral session. The integral dose rates varied from 5-25 W. Some of these dose rates caused convulsions in the monkeys. The radiation was shown to exert no significant effect on the discrimination task, whereas a dose-dependent deficit in performance was observed in the repeated acquisition task. Cunitz et al., [1979] trained two rhesus monkeys to move a lever in different directions depending on the lighting conditions in the exposure cage in order to obtain food reinforcement on a fixed ratio schedule. After the animals' performance had reached a steady and consistent level, they were irradiated at the head with continuous-wave 383-MHz RFR at different intensities in subsequent sessions. Radiation started 60 min before and during a session of responding. The authors reported a decrease in the rate of correct responding when the SAR at the head reached 22-23 W/kg. In another study, Scholl and Allen [1979] exposed rhesus monkeys to continuous-wave 1200-MHz RFR at SARs of 0.8-1.6 W/kg and observed no significant effect of the radiation on a visual tracking task.

de Lorge [1976] trained rhesus moneys on an auditory vigilance (observing-response) task. The task required continuous sensory-motor activities in which the monkeys had to coordinate their motor responses according to the stimulus cues presented. In the task the monkeys had to press the right lever that produced either a 1070-Hz tone for 0.5 sec or a 2740-Hz tone. The 1070-Hz tone signalled an unrewarded situation. Pressing a left lever when the 2740-Hz tone was on would produce a food reward. Presentation of the higher frequency tone was on a variable interval schedule. After the monkeys had learned to perform the task at a steady level, they were irradiated with 2450-MHz RFR of different intensities. Decreased performance and increased latency time in pressing the left lever were observed when the power density at the head was at 72 mW/cm^2. The deficits could be due to an increase in colonic temperature after exposure to the high intensity RFR.

de Lorge [1979] trained squirrel monkeys to respond to another observing-response task using visual cues. After learning the task, the animals were exposed to 2450-MHz RFR (sinusoidally modulated at 120 Hz) for 30 or 60 min at different power densities (10-75 mW/cm^2) in subsequent sessions. Their performances were disrupted at power densities >50 mW/cm^2. The disruption was power density-dependent and occurred when the rectal temperatures increased more than 1 ^oC. In a more recent experiment, de Lorge [1984] studied rhesus monkeys trained on the auditory vigilance task and the effects of exposure to RFRs of different frequencies (225, 1300, and 5800 MHz). Reduction in performance was observed at different power density thresholds for the frequencies studied: 8.1 mW/cm^2 (SAR 3.2 W/kg) for 225 MHz, 57 mW/cm^2 (SAR 7.4 W/kg) for 1300 MHz, and 140 mW/cm^2 (SAR 4.3 W/kg) for 5800 MHz. de Lorge concluded that the behavioral disruption under different frequencies of exposure was more correlated with change in body temperature. Disruption occurred when the colonic temperature of the animal had increased by 1 ^oC.

Many studies have investigated the effects of RFR on reinforcement schedule-controlled behavior. Sanza and de Lorge [1977] trained rats on a fixed interval schedule for food pellets. After 60 min of exposure to 2450-MHz RFR (modulated at 120 Hz) at 37.5 mW/cm^2, a decrease in response with an abrupt onset was observed. This effect was more pronounced in

rats with a high base line of response rate on the fixed interval schedule. No significant effect on response was observed at power densities of 8.8 and 18.4 mW/cm^2.

D'Andrea et al. [1976] trained rats to bar-press for food at a variable interval schedule. After a constant responding rate was attained, the animals were irradiated with continuous-wave RFRs of 360, 480, or 500 MHz. Bar-press rates were decreased only when the rats were exposed to the 500-MHz radiation at a SAR of approximately 10 W/kg. The animals also showed significant signs of heat stress. In a subsequent study [D'Andrea et al., 1977] RFRs of different frequencies and intensities were studied on their effect on bar-pressing rate on a variable interval schedule. It was found that the latency time of stoppage to respond after the radiation was turned on correlated with the rate of rise in body temperature of the animal. These experiments definitely demonstrated the thermal effect of RFR on operant behavior.

Gage [1979a] trained rats on a variable interval schedule for food reinforcement. Different groups of rats were exposed overnight (15 h) to continuous-wave 2450-MHz RFR at either 5, 10, or 15 mW/cm^2. Responses were tested immediately after exposure. No significant difference in performance was found between the RFR- and sham-exposed rats when exposure was done at an ambient temperature of 22 ^{o}C. However, a power density-dependent reduction in response rate and increase in response duration was found in the RFR-exposed rats when the irradiation was carried out at 28 ^{o}C. At the higher ambient temperature, heat dissipation from the body was less efficient and the exposed rats had higher body temperatures postexposure.

Lebovitz [1980] also studied the effects of pulsed 1300-MHz (1 μs pulses, 600 pps) RFR on rats bar-pressing on a fixed interval schedule for food reinforcement. Both food reinforced bar presses and unrewarded bar presses during the intervals were studied. No significant effect was detected in both types of response at SAR of 1.5 W/kg. However, at 6 W/kg, there was a slight reduction in rewarded bar presses and a large reduction in unrewarded bar presses. The authors concluded that the unrewarded behavior was more susceptible to the effect of RFR than the rewarded behavior. Another related experiment was reported by Sagan and Medici [1979] in which water-deprived chicks were given access to water on fixed intervals irrespective of their responses. During the time between water presentations the chicks showed an increase in motor activity known as 'interim behavior'. Exposure to 450-MHz RFR amplitude-modulated at 3 and 16 Hz at power densities of either 1 or 5 mW/cm^2 during session had no significant effect on the 'interim behavior'.

Effects of RFR on complex operant response sequence and reinforcement schedules were studied in various experiments. de Lorge and Ezell [1980] tested rats on a vigilance behavioral task during exposure to pulsed 5620-MHz RFR and then to pulsed 1280-MHz RFR. In this task, rats had to discriminate two tones in order to press one of two bars appropriately for food reinforcement. Behavioral decrement was observed at an SAR of 2.5 W/kg with the 1280-MHz radiation, but at 4.9 W/kg with the 5620-MHz radiation. Gage [1979b] trained rats to alternate responses between 2 levers at 11-30 times for a food reinforcement. Decrement in response rates was observed after 15 h of exposure to continuous-wave 2450-MHz RFR at 10, 15, and 20 mW/cm^2 (0.3 W/kg per mW/cm^2).

Thomas et al. [1975] trained rats to bar press on two bars: a fixed ratio of 20 on the right bar (20 bar presses produced a food pellet reward) and differential reinforcement of low rate (DRL) on the left bar (bar presses had to be separated by at least 18 sec and no more than 24 sec to produce a reward). There was a time-out period between schedules, i.e., no reinforcement available for responding. Animals were tested 5-10 min after 30 min of exposure to either continuous-wave 2450-MHz, pulsed 2860-MHz (1 μs pulses, 500 pps) or pulsed 9600-MHz (1 μs pulses, 500 pps) RFR at various power densities. An increase in DRL response rate was observed with 2450-MHz radiation >7.5 mW/cm^2 (SAR 2.0 W/kg), 2860-MHz RFR >10 mW/cm^2 (2.7 W/kg), and 9600-MHz RFR >5 mW/cm^2 (SAR 1.5 W/kg). A decrease in the rate of response at the fixed ratio schedule was seen in all three

frequencies when the power density was greater than 5 mW/cm^2. In addition, an increase in response rate was observed during time-out periods under irradiation of the three frequencies of RFR at greater than 5 mW/cm^2.

In another study, Thomas et al. [1976] trained rats to bar press on a tandem schedule using 2 bars. Pressing the right bar for at least 8 times before pressing the left bar would give a food pellet reward. A power density-dependent decrease in the percentage of making 8 or more consecutive responses on the right bar before pressing the left bar was observed in the animals after 30 min of exposure to pulsed 2450-MHz RFR (1 μs pulses, 500 pps) at power densities of 5, 10, and 15 mW/cm^2.

Schrot et al [1980] also trained rats to learn a new daily sequence of pressing of three bars for food reinforcement. An increased number of errors and decreased learning rates were observed in the animals after 30 min of exposure to pulsed 2800-MHz RFR (2 μs pulses, 500 pps) at average power densities of 5 and 10 mW/cm^2 (SARs 0.7 and 1.7 W/kg, respectively). No significant effect on performance was observed at power densities of 0.25, 0.5, and 1 mW/cm^2.

Several studies investigated the effects of chronic RFR exposure on schedule controlled-behavior. Mitchell et al. [1977] trained rats to respond on a mixed schedule of reinforcement (FR-5 EXT-15 sec), in which 5 responses would give a reward and then a 15 sec lapse time (extinction period) was required before a new response would be rewarded. In addition, the schedule of reinforcement was effective when a lamp was on, while no reinforcement was given when the lamp was off. Rats were then exposed to 2450-MHz RFR (average SAR 2.3 W/kg) for 22 weeks (5 h/day, 5 days/week) and tested at different times during the exposure period. The RFR-exposed rats showed higher responses during the extinction period, indicating poorer discrimination of the response cues. In another also pretrained task, rats had to press a bar to postpone the onset of unsignalled electric footshocks (unsignalled avoidance paradigm). No significant difference in performance of this task was observed between the RFR- and sham-exposed animals.

Two series of well-designed experiments were run by D'Andrea et al. [1986a,b] to investigate the effects of chronic RFR exposure on behavior. In one experiment, rats were exposed for 14 weeks (7 h/day, 7 days/week) to continuous-wave 2450-MHz RFR at 2.5 mW/cm^2 (SAR 0.7 W/kg). Decrease in the threshold of electric foot shock detection (i.e., increase in sensitivity) was observed in the irradiated rats during the exposure period. Increased open-field exploratory behavior was observed in the rats at 30 days postexposure. After exposure, the rats were trained to bar press on an interresponse time criterion (IRT). In this schedule, the animals had to respond within 12 to 18 sec after the previous response in order to receive a food reward. Radiofrequency radiation exposed rats emitted more responses during the training period. When the training was completed, the RFR-exposed rats had lower efficiency in bar-pressing to obtain food pellets, i.e., they made more inappropriate responses and received fewer food pellets than the sham-exposed rats during a session. In a signalled two-way active avoidance shuttlebox test, the RFR-exposed rats showed less avoidance response than the sham-exposed rats during training; however, no significant difference in responses in the shuttlebox test was detected at 60 days after exposure between the RFR- and sham-exposed animals. In another series of experiments, rats were exposed to 2450-MHz RFR at 0.5 mW/cm^2 (SAR 0.14 W/kg) for 90 days (7 h/day, 7 days/week). Open-field behavior, shuttlebox performance, and IRT schedule-controlled bar-pressing behavior for food pellets were studied at the end of the exposure period. A small deficit in shuttlebox performance and increased rate of bar-pressing were observed in the RFR exposed rats. Summarizing the data from these two series of experiments [D'Andrea et al., 1986a,b], D'Andrea and his co-workers concluded that the threshold for the behavioral and physiological effects of chronic RFR exposure in the rats studied in their experiments occurred between the power densities of 0.5 mW/cm^2 (SAR 0.14 W/kg) and 2.5 mW/cm^2 (SAR 0.7 W/kg).

D'Andrea et al. [1989] recently studied the behavioral effects of high peak power RFR pulses of 1360-MHz. Rhesus monkeys performing on a complicated reinforcement-schedule involving time-related behavioral tasks (inter-response time, time discrimination, and fixed interval responses) were exposed to high peak power RFR (131.8 W/cm^2 rms, pulse repetition rate 2-32 Hz). No significant disturbance in performance was observed in the monkeys.

Akyel et al. [1991] also studied the effects of exposure to high peak power RFR pulses on behavior. In their experiment, rats pretrained to bar-press for food reinforcement on either fixed ratio, variable interval, or DRL schedule were exposed for 10 min to 1250-MHz pulses. Each pulse (10 μs width) generated a whole body specific absorption of 2.1 J/kg, which corresponds to a whole body average SAR of 0.21 mW/kg. The pulse rate was adjusted to produce different total doses (0.5-14 kJ/kg). Only at the highest dose (14 kJ/kg), stoppage of responding was observed after exposure, when the colonic temperature was increased by ~2.5 °C. Responding resumed when colonic temperature returned to within 1.1 °C above the preexposure level. When responding resumed, the response rates on the fixed ratio and variable interval schedules were below the preexposure base line level. Responses on the DRL schedule were too variable to allow a conclusion to be drawn. The authors concluded that the effect of the high peak power RFR pulses on schedule-controlled behavior was due to hyperthermia.

Behavior conditioning using different reinforcement schedules generates stable base line responses with reproducible patterns and rates. The behavior can be maintained over a long period of time (hrs) and across different experimental sessions. Thus, schedule-controlled behavior provides a powerful means for the study of RFR-behavior interaction in animals. On the other hand, the behavior involves complex stimulus-response interactions. It is difficult to conclude from the effects of RFR on schedule-controlled behavior the underlying neural mechanisms involved.

In a sense, these studies of RFR are similar to those of psychoactive drugs. A large volume of literature is available on the latter topic. A review of the literature on the effects of psychoactive drugs on schedule-controlled behavior reveals the complexity of the interaction and the limitation in data interpretation. In general, the effects of psychoactive drugs on schedule-controlled behavior is dose-dependent. In many cases, especially in behavior maintained by positive reinforcement, an inverted-U-function has been reported, i.e., the behavior is increased at low doses and decreased at high doses of the drug. In addition, the way that a certain drug affects schedule-controlled behavior depends on three main factors: (a) the base line level and pattern of responding of the animal: a general rule is that drugs tend to decrease the rate when the base line responding rate is high and vice versa. This is known as rate-dependency and is true with psychomotor stimulants, major and minor tranquilizers, sedative-hypnotics, and narcotics; (b) the schedule of reinforcement: in addition to its effect on the base line responding rate, a reinforcement schedule can have other specific effects on responses. For example, amphetamine has different effects on responses maintained on DRL schedule and punishment-suppressed responding schedule, even though both schedules generate a similar low response rate; and (c) the stimulus-control involved in the study: e.g., responses maintained by electric shock are more resistant to drug effects than responses maintained by positive reinforcers. On the other hand, some drugs have differential effects on signalled-avoidance versus continuous avoidance responding.

Thus, to fully understand the effect of RFR, the parameters of the radiation (different dose rates, frequency, duration of exposure, etc.), different reinforcement-schedules, and conditioning procedures have to be carefully studied and considered. However, there is evidence that the above determining factors on schedule-controlled behavior may also hold in the case of RFR. Exposure to RFR caused a decrease in response rate when a variable interval schedule that produces a steady rate of responding was used [D'Andrea et al., 1976; 1977; Gage, 1979a], and an increase in responding when the DRL-schedule of reinforcement

was used [Thomas et al., 1975]. This may reflect the rate-dependency effect. On the other hand, stimulus control as a determinant of response outcome was seen in the study of Lebovitz [1980] when unrewarded responses were disrupted more by RFR than rewarded responses, and the study of Hunt et al. [1975] that showed the reverse relationship. In the former experiment a fixed interval schedule was used, whereas in the latter a discrimination paradigm was studied.

Another related point is that most psychoactive drugs affect body temperature. Stimulants cause hyperthermia, barbiturates cause hypothermia, and narcotics have a biphasic effect on body temperature (hyperthermia at low doses and hypothermia at high doses). It is not uncommon to observe a change of 2-3 ^{o}C within 30 min after a drug is administered. However, in reviewing the literature, there is no general correlation between the effects of the drugs on body temperature and schedule-controlled behavior. Thus, body temperature may not be an important factor in an animal's responding under schedule-controlled behavior, at least in the case of psychoactive drugs. On the contrary, some of the experiments described above strongly suggest the role of hyperthermia on the RFR effect on the behavior. Perhaps, a sudden and large increase in body temperature as in the case of RFR can have a major effect on responding.

Generally speaking, when effects were observed, RFR disrupted operant behavior in animals such as in the cases of discrimination responding [de Lorge and Ezell, 1980; Hunt et al., 1975; Mitchell et al., 1977], learning [Lai, 1989b; Schrot et al., 1980], and avoidance [D'Andrea et al., 1986a,b]. This is especially true when the task involved complex schedules and response sequence. In no case has an improvement in operant behavior been reported after RFR exposure. It is interesting that only disruptions in behavior by RFR exposure are reported. In the studies on EEG, both excitation (desynchronization) and depression (synchronization) have been reported after exposure to RFR [Bawin et al., 1979; Chizhenkova, 1988; Chou et al., 1982b; Dumansky and Shandala, 1976; Goldstein and Sisko, 1974; Dumansky and Shandala, 1976; Takeshima et al., 1979]. Motor activity has also been reported to increase [D'Andrea et al., 1979, 1980; Hunt et al., 1975; Mitchell et al., 1977; Rudnev et al., 1978] and decrease [Johnson et al., 1983; Mitchell et al., 1988; Moe et al., 1976; Rudnev et al., 1978] after RFR exposure. If these measurements can be considered as indications of electrophysiological and behavioral arousal and depression, improvement in operant behavior should occur under certain conditions of RFR exposure. This is especially true with avoidance behavior. Psychomotor stimulants that cause EEG desynchronization and motor activation improve avoidance behavior, whereas tranquilizers that have opposite effects on EEG and motor activity decrease avoidance behavior.

GENERAL DISCUSSION

After reviewing the studies on the effects of RFR on the central nervous system, one obvious question comes to my mind: "What is the mechanism responsible for the effects reported?" In most cases, especially the in vivo studies in which high intensities of irradiation were used resulting in an increase in body temperature, thermal effect is most likely the answer. Even in cases when no significant change in body temperature was detected, thermal effect cannot be excluded. An animal can maintain its body temperature by actively dissipating the heat load from the radiation. Activation of thermoregulatory mechanisms can lead to neurochemical, physiological, and behavioral changes. Temperature can be better controlled during in vitro studies. Uneven heating of the sample can still generate temperature gradients, which may affect the normal responses of the specimen studied. However, several points raised by some experiments suggest that the answer is not a simple one. They are: (a) 'Heating controls' do not produce the same effect of RFR [D'Inzeo et al., 1988; Seaman and Wachtel, 1978; Synder, 1971; Johnson and Guy, 1971; Wachtel et al., 1975]; (b) Window

effects are reported [Bawin et al., 1975, 1979; Blackman et al., 1979, 1980a,b, 1989; Chang et al., 1982; Dutta et al., 1984, 1989, 1992; Lin-Liu and Adey, 1982; Oscar and Hawkins, 1977; Sheppard et al., 1979]; (c) Modulated or pulsed RFR is more effective in causing an effect or elicits a different effect when compared with continuous-wave radiation of the same frequency [Arber and Lin, 1985; Baranski, 1972; Frey et al., 1973, 1975; Oscar and Hawkins, 1977; Sanders et al., 1983]; (d) Different frequencies of RFR produce different effects [D'Andrea et al., 1979, 1985; de Lorge and Ezell, 1980; Sanders et al., 1984; Thomas et al., 1975]; and (e) Different exposure orientations or systems of exposure produce different effects at the same average whole body SAR [Lai et al., 1984a, 1988].

I think most of these effects can be explained by the following factors:

1. The physical properties of RFR absorption in the body and the mechanisms by which RFR affects biological functions were not fully understood. In addition, use of different exposure conditions make it difficult to compare the results from different experiments.

2. Characteristics of the response system, i.e., the dependent variable, were not fully understood. In many cases, the underlying mechanism of the response system studied was not known.

3. Dose-response relationship was not established in many instances and conclusions were drawn from a single RFR intensity or exposure duration.

It is well known that the distribution of RFR in an exposed object depends on many factors such as frequency, orientation of exposure, dielectric constant of the tissue, etc. D'Andrea et al. [1987] and McRee and Davis [1984] pointed out the uneven distribution of energy absorbed in the body of an exposed animal with the existence of 'hot spots'. In experiments studying the central nervous system, Williams et al. [1984d] also reported a temperature gradient in the brain of rats exposed to RFR. Structures located in the center of the brain, such as the hypothalamus and medulla, had higher temperatures than peripheral locations, such as the cerebral cortex. In a study by Chou et al. [1985a], comparisons were made of the local SARs in eight brain sites of rats exposed under seven exposure conditions, including exposure in a circular waveguide with the head or tail of an animal facing the radiation source, near field and far field exposures with either E- or H-field parallel to the long-axis of the body, and dorsal exposure in a miniature anechoic chamber with E- or H-field parallel to the long axis of the body. Statistical analysis of the data showed that a) there was a significant difference in local SARs in the eight brain regions measured under each exposure condition, and b) the pattern of energy absorption in different regions of the brain depended on the exposure condition. However, it must be pointed out that in another study [Ward et al., 1986], no temperature 'hot spots' were detected in the brains of rat carcasses and anesthetized rats after irradiation with 2450-MHz RFR. Temperature increases in various regions of the brain were found to be uniform and dependent on the power density of the radiation.

A question that one might ask is whether different absorption patterns in the brain or body could elicit different biological responses in the animal. If this is positive, possible outcomes from the study of bioelectromagnetics research are: (1) a response will be elicited by some exposure conditions and not by others, and (2) different response patterns are elicited by different exposure conditions, even though the average dose rates in the conditions are equal. We [Lai et al., 1984a] reported a difference in responses to the hypothermic effects of pentobarbital depending on whether the rat was exposed with its head facing toward or away from the source of radiation in the waveguide with the average whole body SAR under both conditions remaining the same; however, the patterns of energy absorption in the body and the brain differed in the two exposure conditions. Studies of HACU activity in the different regions of the brain [Lai et al., 1988] also showed that different responses could be triggered using different exposure systems or different waveforms of RFR (continuous-wave or pulsed) with the average whole body SAR held constant under each exposure condition.

These data indicate that the energy distribution in the body and other properties of the radiation can be important factors in determining the outcome of the biological effects of RFR. A series of studies by Frei et al. [1989a,b] also demonstrated some interesting results on this issue. The effects of high intensity 2450- and 2800-MHz RFRs on heart rate, blood pressure, and respiratory rate in ketamine-anesthetized rats were studied. Both frequencies produced increases in heart rate and blood pressure and no significant difference was observed whether continuous-wave or pulsed radiation was used. A difference was observed, however, when the animals were exposed with their bodies parallel to the H- or E-field. In the case of 2450-MHz RFR, the E-orientation exposure produced greater increases in heart rate and blood pressure than the H-orientation exposure; whereas no significant difference in the effects between the two exposure orientations was observed with the 2800-MHz radiation. The authors speculated that the differences could be attributed to the higher subcutaneous temperature and faster rise in colonic temperature in the E-orientation when the rats were exposed at 2450 MHz than at 2800 MHz. Once again, this points out that subtle differences in exposure parameters could lead to different responses. Therefore, due to the peculiar pattern of energy deposition and heating by RFR, it may be impossible to replicate the thermal effect of RFR by general heating, i.e., use of temperature controls.

The fact that dosimetry data were based on stationary models that usually show discrete patterns of energy absorption, further complicate the matter. In animal studies, unless the animal is restrained, the energy absorption pattern changes during the exposure period depending on the position and the orientation of the animal. A possible solution would be to perform long-term exposure experiments, thus, the absorption pattern on the average would be made more uniform.

Another important consideration regarding the biological effects of RFR is the duration or number of exposure episodes. This is demonstrated by the results of some of the studies on the neurological effects of RFR. Depending on the responses studied in the experiments, several outcomes could result: an effect was observed only after prolonged (or repeated) exposure, but not after acute exposure [Baranski, 1972; Baranski and Edelwejn, 1968, 1974; Mitchell et al., 1977; Takashima et al., 1979], an effect disappeared after prolonged exposure suggesting habituation [Johnson et al., 1983; Lai et al., 1987c, 1992a], and different effects were observed after different durations of exposure [Baranski, 1972; Dumanski and Shandala, 1974; Grin, 1974; Lai et al., 1989a, 1989b; Servantie et al., 1974; Snyder, 1971]. All of these different responses reported can be explained as being due to the different characteristics of the dependent variable studied. An interesting question related to this is whether or not intensity and duration of exposure interact, e.g., can exposure to a low intensity over a long duration produce the same effect as exposure to a high intensity radiation for a shorter period?

Thus, even though the pattern or duration of RFR exposure is well-defined, the response of the biological system studied will still be unpredictable if we lack sufficient knowledge of the response system. In most experiments on the neurological effects of RFR, the underlying mechanism of the dependent variable was not fully understood. The purpose of most of the studies was to identify and characterize possible effects of RFR rather than the underlying mechanisms responsible for the effects. This lack of knowledge of the response system studied is not uncommon in biological research. In this regard, it may be appropriate to compare the biological and neurological effects of RFR with those of ethanol. Both entities exert non-specific effects on multiple organs in the body. Their effects are nonspecific, because both ethanol and RFR are not acting on specific receptors. The biological effects of ethanol could be a general action on cell membrane fluidity.

In reviewing the literature on the neurological effects of ethanol, one notices some similarity with those of RFR. In both cases, a wide variety of neurological processes were reported to be affected after exposure, but without a known mechanism. On the other hand, inconsistent data were commonly found. For example, in the case of the effects of ethanol on

dopamine receptors in the brain, an increase [Hruska, 1988; Lai et al., 1980], a decrease [Lucchi et al., 1988; Syvalahti et al., 1988], and no significant change [Muller, 1980; Tabakoff and Hoffman, 1979] in receptor concentration have been reported by different investigators. Such inconsistencies have existed since the late 70's and there has been no satisfactory explanation for them. Similar research findings of increase, decrease, and no significant change in the concentration of muscarinic cholinergic receptors in the cerebral cortex of animals treated with ethanol have also been reported in the literature [Kuriyama and Ohkuma, 1990]. Dosage and route of ethanol treatment, the frequency of administration, and the species of animal studied, etc., could all attribute to variations in the findings [Keane and Leonard, 1989]. As we have discussed earlier, such considerations on the parameters of treatment also apply to the study of the biological effects of RFR. These are further complicated by the special properties of the radiation, such as waveform and modulation. In addition, RFR effects could have rapid onset and offset when the source was turned on and off, whereas the biological effect of ethanol depends on the rates of absorption and metabolism.

Thus, an understanding of the response characteristics of the dependent variables to different parameters of RFR, such as power density, frequency, waveform, etc., is important. Lack of knowledge about such characteristics may explain some of the discrepancies in bioelectromagnetics research results in the literature. Non-linear response characteristics are frequently observed in biological systems, because different mechanisms are involved in producing a response. For example, in the case of apomorphine-induced locomotor activity, a low dose of apomorphine (e.g., 0.1 mg/kg) decreases locomotor activity, whereas a higher dosage (e.g., 1.0 mg/kg) of the drug causes a profound enhancement. A dose in between may cause an insignificant effect. An explanation for this phenomenon is that a low dose of apomorphine activates selectively presynaptic dopamine receptors in the brain, which decreases dopamine release from its terminals and, thus, a decrease in motor activity. At a high dose, apomorphine stimulates the postsynaptic dopamine receptors, leading to an increase in motor activity.

Another common response-characteristic is the inverted-U function. In this situation, a response is only seen at a certain dose range and not at higher or lower dosages. An example of an inverted-U dose-response function is the effect of benzodiazepines on schedule controlled operant behavior. There is not a good explanation for the occurrence of this function. One possible explanation might be that at least two mechanisms, a facilitatory and an inhibitory function, are involved in the response. At a lower dose range of the drug, for example, the facilitatory mechanism predominates and leads to enhancement of the response, whereas, as the dosage increases an inhibitory mechanism is activated, leading to a decline in response. Thus, it is essential that the dose-response function be determined.

The inverted-U response-characteristic can be the basis of some of the 'window' effects reported in bioelectromagnetics research. Thus, with the above considerations, it is not surprising that RFR can cause enhancement, decrement, and no significant effect on a particular response depending upon the exposure conditions. Blackman et al. [1991] stated on the effect of temperature on calcium ion efflux from brain tissue that, "... either outcome (*inhibition or enhancement in release of calcium ions*), or a null result, is possible, depending on the temperature of tissue sample before and during exposure". However, it must be pointed out that the inverted-U function is not sufficient to account for the 'multiple window' effect reported in one of Blackman's studies [Blackman et al., 1989].

Another important consideration in the study of the central nervous system should be mentioned here. It is well known that the functions of the central nervous system can be affected by activity in the peripheral nervous system. Thirty years ago, McAfee [1961, 1963] pointed out that the thermal effect of RFR on the peripheral nervous system can lead to changes in central nervous system functions and behavior in the exposed animal. This is especially important in the in vivo experiments when the whole body is exposed. However,

in most experiments studying the effects of RFR on the central nervous system, the possibility of contribution from the peripheral nervous system was not excluded in the experimental design. Therefore, caution should be taken in concluding that a neurological effect resulted solely from the action of RFR on the central nervous system.

An interesting question arose, whether or not RFR could produce 'non-thermal' biological effects. Many have speculated whether RFR can directly affect the activity of excitable tissues. Schwan [1971, 1977] pointed out that it would take a very high intensity of RFR to directly affect the electrical activity of a cell. On the other hand, Wachtel et al. [1975] have speculated that an RFR-induced polarized current in the membrane of a neuron could lead to changes in activity. Adey [1988] has suggested that cooperative processes in the cell membrane might be reactive to the low energy of oscillating electromagnetic field, leading to a change in membrane potential. Pickard and Barsoum [1988] recorded from cells of the Characeae plant exposed to 0.1-5 MHz pulsed RFR and observed a slow and fast component of change in membrane potential. The slow component was temperature dependent and the fast component was suggested to be produced by rectification of the oscillating electric field induced by RFR on the cell membrane. However, the effect disappeared when the frequency of radiation reached ~10 MHz.

An extreme example of the direct interaction of electromagnetic radiation with a specific biological molecule triggering a neurological effect is the rhodopsin molecules in the rod photorecepter cells that transduce light energy into neural signals. In 1943, a psychophysical experiment by Hecht et al. [1942] suggested that a single photon could activate a rod cell. The molecular biology of rhodopsin is now well understood. It is now known that a single photon can activate a single molecule of rhodopsin. A photon of the visible spectrum turns 11-cis retinol, a moiety of the rhodopsin molecule, to an all-trans form. This triggers a cascade of molecular activities involving specific G-protein, the conversion of cyclic-GMP to 5'-GMP, and eventually closing the sodium-ion channels on the cell membrane of the rod cell. This cascade action leads to a powerful amplification of the photon signal. It was estimated that one photon can affect several hundred C-GMP molecules. Such change is enough to hyperpolarize a rod cell and lead to signal transmission through its synapse [Liebman et al., 1987; Stryer, 1987]. Can a similar molecular sensitive to RFR exist? The problem is that RFR energy is several orders of magnitude ($\sim 10^6$) lower than that of a photon at the visual spectrum. It is difficult to visualize a similar molecular mechanism sensitive enough to detect RFR.

Another consideration is that the ambient level of RFR is very low in the natural environment and could not have generated enough selection pressure for the evolutionary development of such a molecular mechanism. On the other hand, there may be some reason for the development of a molecular mechanism for the detection of static or low frequency electric or magnetic fields. An example is the electroreception mechanism of two Australian monotremes, the platypus, *Ornithorhynchus anatinus*, and the echidna, *Tachyglossus aculeatus* [Gregory et al., 1989a,b; Iggo et al., 1992; Scheich et al., 1986]. Apparently, receptors sensitive to low-level electric fields exist in the snout and bill of these animals, respectively. Electrophysiological recordings from the platypus show that receptors in the bill can be sensitive to a static or sinusoidally changing (12-300 Hz) electric field of 4-20 mV/cm, and cells in the cerebral cortex can respond to a threshold field of 300 μV/cm. Moreover, behavioral experiments showed that the platypus can detect electric fields as small as 50 μV/cm. In the echidna snout, receptors can respond to fields of 1.8-73 mV/cm. These neural mechanisms enable the animals to detect muscular movements of their prey, termites and shrimps. It would be interesting to understand the transduction mechanism in the electroreceptors in these animals. However, it remains to be seen whether RFR can generate a static or ELF field in tissue and that a similar electroreceptor mechanism exists in other mammals.

Another possible explanation suggested for the neurological effects of RFR is stress. This hypothesis has been proposed by Justesen et al. [1973] and Lu et al. [1980] and based on high intensity of exposure. We have also proposed recently that low-level RFR may be a 'stressor' [Lai et al., 1987a]. Our speculation is based on the similarity of the neurological effects of known stressors (e.g., body-restraint, extreme ambient temperature) and those of RFR (see Table 1 in Lai et al., 1987a). Our recent experiments suggesting that low-level RFR activates both endogenous opioids and corticotropin-releasing factor in the brain further support this hypothesis. Both neurochemicals are known to play important roles in an animal's responses to stressors [Amir et al., 1980; Fisher, 1989]. However, it is difficult to prove that an entity is a stressor, since the criteria of stress are not well defined and the caveat of stress is so generalized that it has little predictive power on an animal's response.

In conclusion, I believe the questions on the biological effects of RFR and the discrepancies in research results in the literature can be resolved by (a) a careful and thorough examination of the effects of the different radiation parameters, and (b) a better understanding of the underlying mechanisms involved in the responses studied. With these considerations, it is very unlikely that the neurological effects of RFR can be accounted for by a single unifying neural mechanism.

ACKNOWLEDGMENTS

The author's research was supported by a grant from the National Institute of Environmental Health Sciences (ES-03712). I thank Mrs. Monserrat Carino, Dr. Chung-Kwang Chou, and Dr. Akira Horita for reviewing the manuscript, and especially Mrs. Dorothy Pratt for her patience and endurance in typing and editing the manuscript numerous times.

REFERENCES

Adair, E.R., 1983, "Microwaves and Thermoregulation," Academic Press, New York, NY.

Adey, W.R., 1988, The cellular microenvironment and signalling through cell membrane, *in*: "Electromagnetic fields and Neurobehavioral Functions," M.E. O'Connor and R.H. Lovely, eds., *Prog Clin Biol Res* 257:265-288.

Adey, W.R., Bawin, S.M. and Lawrence, A.F., 1982, Effects of weak amplitude-modulated microwave fields on calcium efflux from awake cat cerebral cortex, *Bioelectromagnetics* 3:295-307.

Akyel, Y., Hunt, E.L., Gambrill, C., Varga, Jr. C., 1991, Immediate postexposure effects of high-peak-power microwave pulses on operant behavior of Wistar rats, *Bioelectromagnetics* 12:183-195.

Albert, E.N., 1977, Light and electron microscopic observations on the blood-brain barrier after microwave irradiation, *in*: "Symposium on Biological Effects and Measurement of Radio Frequency Microwaves," D.G. Hazzard, ed., HEW Publication (FDA) 77-8026, Rockville, MD.

Albert, E.N., 1979a, Reversibility of microwave induced blood-brain barrier permeability, *Radio Sci* 14:323-327.

Albert, E.N., 1979b, Current status of microwave effects on the blood-brain barrier, *J Microwave Power* 14:281-285.

Albert, E.N., and DeSantis, M., 1975, Do microwaves alter nervous system structure? *Ann NY Acad Sci* 247:87-108.

Albert, E.N., and DeSantis, M., 1976, Histological observations on central nervous system, *in*: "Biological Effects of Electromagnetic Waves," vol. 1, C.C. Johnson and M.C. Shore, eds., HEW Publication (FDA) 77-8010, Rockville, MD.

Albert, E.N., and Kerns, J.M., 1981, Reversible microwave effects on the blood-brain barrier, *Brain Res* 230:153-164.

Albert, E.N., and Sherif, M., 1988, Morphological changes in cerebellum of neonatal rats exposed to 2.45 GHz microwaves, *in*: "Electromagnetic Fields and Neurobehavioral Functions," M.E. O'Connor and R.H. Lovely, eds., *Prog Clin Biol Res* 257: 135-151.

Albert, E.N., Sherif, M.F., and Papadopoulos, N-J., 1981a, Effects of non-ionizing radiation on the Purkinje cells of the uvula in squirrel monkey cerebellum, *Bioelectromagnetics* 2:241-246.

Albert, E.N., Sherif, M.F., Papadopoulos, N.J., Slaby, F.J., and Monahan, J., 1981b, Effect of nonionizing radiation on the Purkinje cells of the rat cerebellum, *Bioelectromagnetics* 2:247-257.

Altman, J., 1975, Effects of interference with cerebellar maturation on the development of locomotion: an experimental model of neurobehavioral retardation, *in*: "Brain Mechanisms in Mental Retardation," N.A. Buchwald and M.A.B. Brazier, eds., Academic Press, New York, NY.

Amir, S., Brown, Z.W., and Amit, Z., 1980, The role of endorphins in stress: evidence and speculations, *Neurosci Biobehav Rev* 4:77-86.

Arber, S.L., and Lin, J.C., 1985, Microwave-induced changes in nerve cells: effects of modulation and temperature, *Bioelectromagnetics* 6:257-270.

Ashani, Y., Henry, F.H., and Catravas, G.N., 1980, Combined effects of anticholinesterase drugs and low-level microwave radiation, *Radiat Res* 84:469-503.

Atweh, S., Simon, J.R., and Kuhar, M.J., 1975, Utilization of the sodium-dependent high-affinity choline uptake in vitro as a measure of activity of cholinergic neurons in vivo, *Life Sci* 17:1534-1544.

Baranski, S., 1972, Histological and histochemical effects of microwave irradiation on the central nervous system of rabbits and guinea pigs, *Am J Physiol Med* 51:182-190.

Baranski, S., and Edelwejn, Z., 1968, Studies on the combined effects of microwaves and some drugs on bioelectric activity of the rabbit central nervous system, *Acta Physiol Polon*, 19:37-50.

Baranski, S., and Edelwejn, Z., 1974, Pharmacological analysis of microwave effects on the central nervous system in experimental animals, *in*: "Biological Effects and Health Hazards of Microwave Radiation: Proceedings of an International Symposium," P. Czerski, et al., eds., Polish Medical Publishers, Warsaw.

Bawin, S.M., Gavalas-Medici, R.J., and Adey, W.R., 1973, Effects of modulated very high frequency fields on specific brain rhythms in cats, *Brain Res* 58:365-384.

Bawin, S.M., Kaczmarek, L.K., and Adey, W.R., 1975, Effects of modulated VHF fields on the central nervous system, *Annals NY Acad Sci* 247:74-81.

Bawin, S.M., Adey, W.R., and Sabbot, I.M., 1978, Ionic factors in release of $^{45}Ca^{2+}$ from chicken cerebral tissue by electromagnetic fields, *Proc Nat'l Acad Sci USA* 75:6314-6318.

Benson, E.B., Lange, D.G., Fujimoto, J.M., and Ishi, T.K., 1983, Effects of acute microwave irradiation on phenobarbital sleep and disposition to brain in mice, *J Toxicol Environ Health* 11:261-274.

Bermant, R.I., Reeves, D.L., Levinson, D.M., and Justesen, D.R., 1979, Classical conditioning of microwave-induced hyperthermia in rat, *Radio Sci* 14(6):201-207.

Blackman, C.F., Elder, J.A., Weil, C.M., Benane, S.G., Eichinger, D.C., and House, D.E., 1979, Induction of calcium-ion efflux from brain tissue by radio-frequency radiation: effects of modulation frequency and field strength, *Radio Sci* 14:93-98.

Blackman, C.F., Benane, S.G., Elder, J.A., House, D.E., Lampe, J.A., and Faulk, J.M., 1980a, Induction of calcium ion efflux from brain tissue by radiofrequency radiation: effect of sample number and modulation frequency on the power-density window, *Bioelectromagnetics* 1:35-43.

Blackman, C.F., Benane, S.G., Joines, W.T., Hollis, M.A., and House, D. E., 1980b, Calcium ion efflux from brain tissue: power density versus internal field-intensity dependencies at 50-MHz RF radiation, *Bioelectromagnetics* 1:277-283.

Blackman, C.F., Benane, S.G., House, D.E., and Joines, W.T., 1985, Effects of ELF (1-120 Hz) and modulated (50 Hz) RF field on the efflux of calcium ions from brain tissue, in vitro, *Bioelectromagnetics* 6:1-11.

Blackman, C.F., Benane, S.G., Elliot, D.J., House, D.E., and Pollock, M.M., 1988, Influence of electromagnetic fields on the efflux of calcium ions from brain tissue, in vivo: a three-model analysis consistent with the frequency response up to 510 Hz, *Bioelectromagnetics* 9:215-227.

Blackman, C.F., Kinney, L.S., House, D.E., and Joines, W.T., 1989, Multiple power density windows and their possible origin, *Bioelectromagnetics* 10:115-128.

Blackman, C.F., Benane, S.G., and House, D.E., 1991, The influence of temperature during electric and magnetic-field induced alteration of calcium-ion release from in vitro brain tissue, *Bioelectromagnetics* 12:173-182.

Blackwell, R.P., 1980, Effects of microwave exposure on anesthesia in the mouse, *in*: "Proceeding on the International Symposium on the Biological Effects of Electromagnetic Waves," UNSI, CNFRS, Jouy en Josas, France.

Blasberg, R.G., 1979, Problems of quantifying effects of microwave irradiation on the blood-brain barrier, *Radio Sci* 14(6):335-344.

Bolwig, T.G., 1988, Blood-brain barrier studies with special reference to epileptic seizure, *Acta Psychiatr Scand* 78(345):15-20.

Bracstrup, C., and Squires, R.F. , 1978, Pharmacological characterization of benzodiazepine receptors in the brain, *Eur J Pharmac* 48:263-270.

Braestrup, C., Neilsen, M., Neilsen, E.B., and Lyon, M., 1979, Benzodiazepine receptors in the brain as affected by different experimental stresses: the changes are small and not unidirectional, *Psychopharmacology* 65:273-277.

Bruce-Wolfe, V., and Justesen, D.R., 1985, Microwaves retard the anesthetic action of pentobarbital, *Abstr Ann Meeting Bioelectromagnetics Soc* 7:47.

Carroll, D.R., Levinson, D.M., Justesen, D.R., and Clarke, R.L., 1980, Failure of rats to escape from a potentially lethal microwave field, *Bioelectromagnetics* 1:101:115.

Catravas, C.N., Katz, J.B., Takenaga, J., and Abbott, J.R., 1976, Biochemical changes in the brain of rats exposed to microwaves of low power density (symposium summary), *J Microwave Power* 11:147-148.

Chamness, A.F., Scholes, H.R., Sexauer, S.W., and Frazer, J.W., 1976, Metal ion content of specific areas of the rat brain after 1600-MHz radiofrequency irradiation, *J Microwave power* 11:333-337.

Chang, B.K., Huang, A.T., Joines, W.T., and Kramer, R.S., 1982, The effect of microwave radiation (1.0 GHz) on the blood-brain barrier, *Radio Sci* 17:165-168.

Chizhenkova, R.A., 1988, Slow potentials and spike unit activity of the cerebral cortex of rabbits exposed to microwaves, *Bioelectromagnetics* 9:337-345.

Chou, C.K. and Galambos, S.R., 1979, Middle ear structures contribute little to auditory perception of microwaves, *J Microwave Power* 14:321-326.

Chou, C.K. and Guy, A.W., 1978, Effects of electromagnetic fields on isolated nerve and muscle preparation, *IEEE Trans Microwave Th Tech* MTT-26:141-147.

Chou, C.K., and Guy, A.W., 1979a, Carbon-loaded Teflon electrodes for chronic EEG recordings in microwave research, *J Microwave Power* 14:399-404.

Chou, C.K. and Guy, A.W., 1979b, Microwave-induced auditory responses in guinea pigs: relationship of threshold and microwave-pulse duration, *Radio Sci* 14(6):193-197.

Chou, C.K., Galambos, R., Guy, A.W., and Lovely, R.H., 1975, Cochlear microphonics generated by microwave pulses, *J Microwave Power* 10:361-367.

Chou, C.K., Guy, A.W., and Galambos, R., 1982a, Auditory perception of radiofrequency electromagnetic fields, *J Acoust Soc Am* 71:1321-1334.

Chou, C.K., Guy, A.W., McDougall, J.B., and Han, L.F., 1982b, Effects of continuous and pulsed chronic microwave exposure on rabbits, *Radio Sci* 17:185-193.

Chou, C.K., Guy, A.W., and Johnson, R.B., 1984, SAR in rats exposed in 2450-MHz circularly polarized waveguide, *Bioelectromagnetics* 5:389-398.

Chou, C.K., Guy, A.W., McDougall, J., and Lai, H., 1985a, Specific absorption rate in rats exposed to 2450-MHz microwaves under seven exposure conditions, *Bioelectromagnetics* 6:73-88.

Chou, C.K., Yee, K.C., and Guy, A.W., 1985b, Auditory response in rats exposed to 2450-MHz electromagnetic fields in a circularly polarized waveguide, *Bioelectromagnetics* 6:323-326.

Cotman, C.W., Brinton, R.E., Jalaburda, A., McEwen, B., and Schneider, D.M., eds., 1987, "The Neuro-Immune-Endocrine Connection," Raven Press, New York, NY.

Cunningham, C.L., Crabbe, J.C., and Rigter, H., 1984, Pavlovian conditioning of drug-induced changes in body temperature, *Pharmac Ther* 23:365-391.

Czerski, P., Ostrowski, K., Shore, M.L., Silverman, C.H., Sues, M.J., and Waldeskog, B., eds., 1974, "Biological Effects and Health Hazard of Microwave Radiation: Proceedings of an International Symposium," P. Czerski, et al., eds., Polish Medical Publisher, Warsaw.

D'Andrea, J.A., Gandhi, O.P., and Kesner, R.P., 1976, Behavioral effects of resonant electromagnetic power absorption in rats, *in*: "Biological Effects of Electromagnetic Waves," vol 1, C.C. Johnson and M.L. Shore, eds., HEW Publication (FDA) 77-8010, Rockville, MD.

D'Andrea, J.A., Gandhi, O.P., and Lords J.L., 1977, Behavioral and thermal effects of microwave radiation at resonant and nonresonant wavelengths, *Radio Sci* 12:251-256.

D'Andrea, J.A., Gandhi, O.P., Lords, J.L., Durney, C.H., Johnson, C.C., and Astle, L., 1979, Physiological and behavioral effects of chronic exposure to 2450-MHz microwaves, *J Microwave Power* 14:351-362.

D'Andrea, J.A., Gandhi, O.P., Lords. J.L., Durney, C.H., Astle, L., Stensaas, L.J., and Schoenberg, A.A., 1980, Physiological and behavioral effects of prolonged exposure to 915 MHz microwaves, *J Microwave Power* 15(2):123-135.

D'Andrea, J.A., DeWitt, J.R., Gandhi, O. P., Stensaas, S., Lords, J.L., and Nielson, H.C., 1986a, Behavioral and physiological effects of chronic 2450-MHz microwave irradiation of the rat at 0.5 mW/cm^2, *Bioelectromagnetics* 7:45-56.

D'Andrea, J.A., DeWitt, J.R., Emmerson, R.Y., Bailey, C., Stensaas, S., and Gandhi, O. P., 1986b, Intermittent exposure of rat to 2450-MHz microwaves at 2.5 mW/cm^2: behavioral and physiological effects, *Bioelectromagnetics* 7:315-328.

D'Andrea, J.A., Emmerson, R.Y., Dewitt, J.R., and Gandhi, O.P., 1987, Absorption of microwave radiation by the anesthetized rat: electromagnetic and thermal hotspots in body and tail, *Bioelectromagnetics* 8:385-396.

D'Andrea, J.A., Cobb, B.L., and de Lorge, J., 1989, Lack of behavioral effects in the rhesus monkey to high peak power microwave pulses at 1.3 GHz, *Bioelectromagnetics* 10:65-76.

da Silva, F.L., 1991, EEG analysis: theory and practice, *in*: "Electroencephalography: Basic Principles, Clinical Applications, and Related Fields," E. Niedermeyer and F.L. da Silva, eds., Urban and Schwargenberg, Baltimore, MD.

Dekker, A.J.A.M., Conner, D.J., and Thal, L.J., 1991, The role of cholinergic projections from the nucleus basalis in memory, *Neurosci Biobehav Rev* 15:299-317.

de Lorge, J.O., 1976, The effects of microwave radiation on behavior and temperature in rhesus monkeys, *in*: "Biological Effects of Electromagnetic Waves," vol. 1, C.C. Johnson and M.L. Shore, eds., HEW Publication (FDA) 77-8010, Rockville, MD.

de Lorge, J.O., 1979, Operant behavior and rectal temperature of squirrel monkeys during 2.45-GHz microwave irradiation, *Radio Sci* 14(6):217-225.

de Lorge, J.O., 1985, Effects of microwaves on schedule-controlled behavior, *in*: "Behavioral Effects of Microwave Radiation Absorption," J.C. Monahan, and J.A. D'Andrea, eds., HHS Publication, FDA 85-8238, U.S. Government Printing Office, Washington, DC.

de Lorge, J., and Ezell, C.S., 1980, Observing-responses of rats exposed to 1.28- and 5.62-GHz microwaves, *Bioelectromagnetics* 1:183-198.

D'Inzeo, G., Bernardi, P., Eusebi, F., Grassi, F., Tamburello, C., and Zani, B.M., 1988, Microwave effects on acetylcholine-induced channels in cultured chick myotubes, *Bioelectromagnetics* 9:363-372.

Dumansky, J.D., and Shandala, M.G., 1974, The biologic action and hygienic significance of electromagnetic fields of super high and ultra high frequencies in densely populated areas, *in*: "Biologic Effects and Health Hazard of Microwave Radiation: Proceedings of an International Symposium," P. Czerski, et al., eds., Polish Medical Publishers, Warsaw.

Dunn, A.J., 1989, Psychoneuroimmunology for the psychoneuroendocrinologist: a review of animal studies of nervous system-immune system interactions, *Psychoneuroendocrinology* 14:251-274.

Dutta, S.K., Subramoniam, A., Ghosh, B., and Parshad, R., 1984, Microwave radiation-induced calcium ion efflux from human neuroblastoma cells in culture, *Bioelectromagnetics* 5:71-78.

Dutta, S.K., Ghosh, B., and Blackman, C.F., 1989, Radiofrequency radiation-induced calcium ion efflux enhancement from human and other neuroblastoma cells in culture, *Bioelectromagnetics* 10:197-202.

Dutta, S.K., Das, K., Ghosh, B., and Blackman, C.F., 1992, Dose dependence of acetylcholinesterase activity in neuroblastoma cells exposed to modulated radio-frequency electromagnetic radiation, *Bioelectromagnetics* (In press).

Eikelboom, R., and Stewart, J., 1982, Conditioning of drug-induced physiological responses, *Psychol Rev* 89:507-528.

Estevez, E.E., Jernsalinsky, D., Medina, J.H., and DeRobertis, E., 1984, Cholinergic muscarinic receptors in rat cerebral cortex, basal ganglia, and cerebellum undergo rapid and reversible changes after acute stress, *Neurosci* 13:1353-1357.

Finkelstein, Y., Koffler, B., Rabey, J.M., and Gilad, G.M., 1985, Dynamics of cholinergic synaptic mechanisms in rat hippocampus after stress, *Brain Res* 343:314-319.

Fisher, L.A., 1989, Corticotropin-releasing factor: endocrine and automatic integration of responses to stress, *Trends Pharmac Sci* 10:189-193.

Frei, M.R., Jauchem, J.R., Padilla, J.M., and Merritt, J.H., 1989a, Thermal and physiological responses of rats exposed to 2.45-GHz radiofrequency radiation: a comparison of E and H orientations, *Radiat Envir Biophys* 28:235-246.

Frei, M.R., Jauchem, J.R., and Padilla, J.M., 1989b, Thermal and physiological changes in rats exposed to CW and pulsed 2.8 GHz radiofrequency radiation in E and H orientations, *Int J Radiat Biol* 56:1033-1044.

Frey, A.H., 1961, Auditory system response to radio frequency energy, *Aerospace Med* 32:1140-1142.

Frey, A.H., 1977, Behavioral effects of electromagnetic energy, *in*: "Symposium on Biological Effects and Measurement of Radio Frequency Microwaves," D.J. Hazzard, ed., HEW Publication (FDA), 77-8026, Rockville, MD.

Frey, A.H., and Feld, S.R., 1975, Avoidance by rats of illumination with low power nonionizing electromagnetic energy, *J Comp Physiol Psychol* 89:183-188.

Frey, A.H., and Wesler, L.S., 1983, Dopamine receptors and microwave energy exposure, *J Bioelectr* 2:145-157.

Frey, A.H., Feld, S.R., and Frey, B., 1975, Neural function and behavior: defining the relationship. *Ann N Y Acad Sci* 247:433-439.

Gage, M.I., 1979a, Microwave irradiation and ambient temperature interact to alter rat behavior following overnight exposure, *J Microwave Power* 14:389-398.

Gage, M.I., 1979b, Behavior in rats after exposure to various power densities of 2450 MHz microwaves, *Neurobehav Toxicol* 1:137-143.

Galloway, W.D., 1975, Microwave dose-response relationship on two behavioral tasks, *Ann N Y Acad Sci* 247:410-416.

Galloway, W.D., and Waxler, M., 1977, Interaction between microwaves and neuroactive compounds, *in*: "Symposium on Biological Effects and Measurement of Radio Frequency Microwaves," D.J. Hazzard, ed., HEW Publication (FDA) 77-8026, Rockville, MD.

Galvin, M.J., Parks, D.L., and McRee, D.L., 1981, Influence of 2.45 GHz microwave radiation on enzyme activity, *Radiat Environ Biophys* 19:149-156.

Galvin, M.J., Tilson, H.A., Mitchell, C.L., Peterson, J., and McRee, D.I., 1986, Influence of pre- and postnatal-exposure of rats to 2.45-GHz microwave radiation on neurobehavioral functions, *Bioelectromagnetics* 7:57-71.

Gandhi, C.R., and Ross, D.H., 1989, Microwave induced stimulation of ^{32} Pi- incorporation into phosphoinositides of rat brain synaptosomes, *Radiat Environ Biophys* 28:223-234.

Gandhi, V.C., and Ross, D.H., 1987, Alteration in a-adrenergic and muscarinic cholinergic receptor binding in rat brain following nonionizing radiation, *Radiat Res* 109:90-99.

Garcia, J., and Koelling, R., 1966, Relation of cue to consequence in avoidance learning, *Psychonom Sci* 4:123-124.

Garcia, J., Ervin, F., and Koelling, R., 1966, Learning with prolonged delay of reinforcement, *Psychonom Sci* 5:121-122.

Goldman, H., Lin, J.C., Murphy, S., and Lin, M.F., 1984, Cerebrovascular permeability to Rb-86 in the rat after exposure to pulsed microwaves, *Bioelectromagnetics* 5:323-330.

Goldstein, L., and Sisko, Z., 1974, A quantitative electro-encephalographic study of the acute effect of X-band microwaves in rabbits, *in*: "Biological Effects and Health Hazards of Microwave Radiation: Proceedings of an International Symposium," P. Czerski, et al., eds., Polish Medical Publishers, Warsaw.

Gordon, Z.V., 1970, Biological effects of microwaves in occupational hygiene, Israel Program for Scientific Translations, Jerusalem, Israel, NASA77F-633, TT70-50087:NTIS N71-14632.

Gregory, J.E., Iggo, A., McIntyre, A.K. and Proske, U., 1989a, Responses of electroreceptors in the platypus bill to steady and alternating potentials, *J Physiol* 408:391-404.

Gregory, J.E., Iggo, A., McIntyre, A.K. and Proske, U., 1989b, Response of electro-receptors in the snout of the echidna, *J Physiol* 414:521-538.

Grin, A.N., 1974, Effects of microwaves on catecholamine metabolism in brain, *US Joint Pub Research Device Rep* JPRS 72606.

Gruenau, S.P., Oscar, K.J., Folker, M.T., and Rapoport, S.I.,1982, Absence of microwave effect on blood-brain barrier permeability to ^{14}C-sucrose in the conscious rat, *Exp Neurobiol* 75:299-307.

Guy, A.W., 1979, Miniature anechoic chamber for chronic exposure of small animals to plane wave microwave field, *J Microwave Power* 14:327-338.

Guy, A.W., Chou, C.K., Lin, J.C., and Christensen, D., 1975, Microwave-induced acoustic effects in mammalian auditory systems and physical materials, *Ann NY Acad Sci* 247:194-215.

Guy, A.W., Wallace, J., and McDougall, J.A., 1979, Circularly polarized 2450-MHz waveguide system for chronic exposure of small animals to microwaves, *Radio Sci* 14(6):63-74.

Hecht, S., Schlaer, S., and Pirene, M.H., 1942, Energy, quanta, and vision, *J Gen Physiol* 25:819-840.

Hjeresen, D.L., Doctor, S.R., and Sheldon, R.L., 1979, Shuttlebox-side preference as mediated by pulsed microwaves and conventional auditory cue, *in*: "Electromagnetic Fields in Biological System," S.S.Stuchly, ed., Ottawa, Canada.

Hjeresen, D.L., Umbarger, K.O., and McElroy, J.F., 1987, Benzodiazepine receptor antagonist RO 15-1788 blocks the 2.45 GHz microwave attenuation of ethanol-induced hypothermia, *Abst Ann Meeting Bioelectromagnetics Soc* 9:25.

Hjeresen, D.L., Francendese, A., and O'Donnell, J.M., 1988, Microwave attenuation of ethanol-induced hypothermia: ethanol tolerance, time cause, exposure duration and dose response studies, *Bioelectromagnetics* 9:63-78.

Hjeresen, D.L., Francendese, A., and O'Donnell, J.M., 1989, Microwave attenuation of ethanol-induced interactions with noradrenergic neurotransmitter systems, *Health Phys* 56:767-776.

Hruska, R.E., 1988, Effect of ethanol administration on striatal D_1 and D_2 dopamine receptors, *J Neurochem* 50:1929-1933.

Hunt, E.L., King, N.W., and Phillips, R.D., 1975, Behavioral effects of pulsed microwave radiation, *Ann NY Acad Sci* 247:440-453.

Iggo, A., Gregory, J.E., and Proske, U., 1992, The central projection of electrosensory information in the platypus, *J Physiol* 447:449-465.

Jauchem, J.R., 1985, Effects of drugs on thermal responses to microwaves, *Gen Pharmacol* 16:307-310.

Jauchem, J.R., Frei, M.R., and Heinmets, F., 1983, Thermal bradycardia during radiofrequency radiation, *Physiol Chem Phys* 15:429-434.

Jauchem, J.R., Frei, M.R., and Heinmets, F., 1984, Increased susceptibility to radiofrequency radiation due to pharmacological agents, *Aviat Space Environ Med* 55:1036-1040.

Jauchem, J.R., Frei, M.R., and Heinmets, F., 1985, Effects of psychotropic drugs on thermal responses to radiofrequency radiation, *Aviat Space Environ Med* 56:1183-1188.

Jenkins, H.M., 1970, Sequential organization on schedules of reinforcement, *in*: "The Theory of Reinforcement Schedules," W.N. Schoenfeld, ed., Appleton-Century-Crofts, New York, NY.

Johnson, C.C., and Guy, A.W., 1972, Nonionizing electromagnetic wave effect in biological materials and systems, *Proc IEEE* 60:692-718.

Johnson, R.B., Meyers, D.E., Guy, A.W., Lovely, R.H., and Galambos, R., 1976, Discriminative control of

appetitive behavior by pulsed microwave radiation in rats, *in*: "Biological Effects of Electromagnetic Waves," vol. 1, C.C. Johnson and M.L. Shore, eds., HEW Publication (FDA) 77-88010, Rockville, MD.

Johnson, R.B., Hamilton, J., Chou, C.K., and Guy, A.W., 1980, Pulsed microwave reduction of diazepam-induced sleeping in the rat, *Abst Ann Meeting Bioelectromagnetrics Soc* 2:4.

Johnson, R.B., Spackman, D., Crowley, J., Thompson, D., Chou, C.K., Kunz, L.L., and Guy, A.W., 1983, Effects of long-term low-level radiofrequency radiation exposure on rats, vol. 4, Open field behavior and corticosterone, USAF SAM-TR83-42, Report of USAF School of Aerospace Medicine, Brooks AFB, San Antonio, TX.

Justesen, D.R., 1980, Microwave irradiation and blood-brain barrier, *Proc IEEE* 68:60-67.

Justesen, D.R., Levinson, D.M., and Justesen, L.R., 1973, Psychogenic stressors are potent mediators of the thermal response to microwave irradiation, *in*: "Biological Effects and Health Hazards of Microwave Radiation: Proceedings of an International Symposium," P. Czerski, et al., eds., Polish Medical Publishers, Warsaw.

Kaplan, J., Polson, R., Rebert, C., Lunan, K., and Gage, M., 1982, Biological and behavioral effect of pre- and post-natal exposure to 2450 MHz electromagnetic radiation in the squirrel monkey, *Radio Sci* 171(5):135-144.

Katoh, A., Nabeshima, T., and Kameyama, T., 1990, Behavioral changes induced by stressful situation: effects of enkephalins, dynorphin, and their interaction, *J. Pharmac Exp Ther* 253:600-607.

Keane, B., and Leonard, B.E., 1989, Rodent models of alcoholism: a review, *Alcohol Alcoholism* 24:299-309.

King, N.W., Justesen, D.R., and Clarke, R.L., 1971, Behavioral sensitivity to microwave irradiation, *Science* 172:398-401.

Kues, H.A., and Monahan, J.C., 1992, Microwave-induced changes to the primate eye, *Johns Hopkins APL Tech Digest* 13:244-254.

Kues, H.A., McLeod, D.S., Monahan, J.C., D'Anna, S.A., and Lutty, G.S., 1990, Retinal changes in the primate following pulsed 2.45-GHz exposures, *Abst Ann Meeting Bioelectromagnetics Soc* 12:22.

Kues, H.A., Monahan, J.C., D'Anna, S.A., McLeod, D.S., Lutty, G.A., and Koslov, S., 1992, Increased sensitivity of the non-human primate eye to microwave radiation following ophthalmic drug pretreatment, *Bioelectromagnetics* (In press).

Kuriyama, K., and Ohkuma, S., 1990, Alteration in the function of cerebral neurotransmitter receptors during the establishment of alcohol dependence: neurochemical aspects, *Alcohol Alcoholism* 25:239-249.

Lai, H., 1987, Acute exposure to noise affects sodium-dependent high-affinity choline uptake in the central nervous system of the rat, *Pharmac Biochem Behav* 28:147-151.

Lai, H., 1992, Research on the neurological effects of nonionizing radiation at the University of Washington, *Bioelectromagnetics* 13:513-526.

Lai, H., and Carino, M.A., 1990a, Effects of noise on high-affinity choline uptake in the frontal cortex and hippocampus of the rat are blocked by intracerebroventricular injection of corticotropin-releasing factor antagonist, *Brain Res* 527:354-358.

Lai, H., and Carino, M.A., 1990b, Acute white noise exposure affects the concentration of benzodiazepine receptors in the brain of the rat, *Pharmacol Biochem Behav* 36:985-987.

Lai, H., Carino, M.A., and Horita, A., 1980, Effects of ethanol on central dopamine functions, *Life Sci* 27:299-304.

Lai, H., Horita, A., Chou, C.K., and Guy, A.W., 1983, Psychoactive drug response is affected by acute low-level microwave irradiation, *Bioelectromagnetics* 4:205-214.

Lai, H., Horita, A., Chou, C.K., and Guy, A.W., 1984a, Acute low-level microwave irradiation and the actions of pentobarbital: effects of exposure orientation, *Bioelectromagnetics* 5:203-212.

Lai, H., Horita, A., Chou, C.K., and Guy, A.W., 1984b, Low-level microwave irradiation affects ethanol-induced hypothermia and ethanol consumption, *Bioelectromagnetics* 5:213-220.

Lai, H., Horita, A., Chou, C.K., and Guy, A.W., 1984c, Microwave-induced postexposure hyperthermia: involvement of endogenous opioids and serotonin, *IEEE Trans Microwave Th Tech* MTT-32:882-886.

Lai, H., Horita, A., Chou, C.K., and Guy, A.W., 1986a., Low-level microwave irradiation attenuates naloxone-induced withdrawal syndrome in morphine-dependent rats, *Pharmac Biochem Behav* 24:151-153.

Lai, H., Horita, A., Chou, C.K., and Guy, A.W., 1986b, Effects of low-level microwave irradiation on amphetamine hyperthermia are blockable by naloxone and classically conditionable, *Psychopharmacology* 88:354-361.

Lai, H., Zabawska, J., and Horita, A., 1986c, Sodium-dependent, high-affinity choline uptake in hippocampus and frontal cortex of the rat affected by acute restraint stress, *Brain Res* 372:366-369.

Lai, H., Horita, A., Chou, C.K., and Guy, A.W., 1987a, A review of microwave irradiation and actions of psychoactive drugs, *IEEE Eng Med Biol* 6(1):31-36.

Lai, H., Horita, A., Chou, C.K., and Guy, A.W., 1987b, Low-level microwave irradiation affects central cholinergic activity in the rat, *J Neurochem* 48:40-45.

Lai, H., Horita, A., Chou, C.K., and Guy, A.W., 1987c, Effects of low-level microwave irradiation on hippocampal and frontal cortical choline uptake are classically conditionable, *Pharmac Biochem Behav* 27:635-639.

Lai, H., Horita, A., and Guy, A.W., 1988, Acute low-level microwave exposure and central cholinergic activity: studies on irradiation parameters, *Bioelectromagnetics*, 9:355-362.

Lai, H., Carino, M.A., Horita, A., and Guy, A.W., 1989a, Acute low-level microwave exposure and central cholinergic activity: a dose-response study, *Bioelectromagnetics*, 10:203-209.

Lai, H., Carino, M.A., and Guy, A.W., 1989b, Low-level microwave irradiation and central cholinergic systems, *Pharmac Biochem Behav* 33:131-138.

Lai, H., Carino, M.A., Horita, A., and Guy, A.W., 1990, Corticotropin-releasing factor antagonist blocks microwave-induced changes in central cholinergic activity in the rat, *Brain Res Bull* 25:609-612.

Lai, H., Carino, M.A., Wen, Y.F., Horita, A., and Guy, A.W., 1991, Naltrexone pretreatment blocks microwave-induced changes in central cholinergic receptors, *Bioelectromagnetics* 12:27-33.

Lai, H., Carino, M.A., Horita, A., and Guy, A.W., 1992a, Single vs repeated microwave exposure: effects on benzodiazepine receptors in the brain of the rat, *Bioelectromagnetics* 13:57-66.

Lai, H., Carino, M.A., Horita, A., and Guy, A.W., 1992b, Opioid receptor subtypes mediating the microwave-induced decreases in central cholinergic activity in the rat, *Bioelectromagnetics* 13:237-247.

Lai, H., Horita, A., and Guy, A.W., 1993, Microwave irradiation affects radial-arm maze performance in the rat, *Bioelectromagnetics* (In press).

Lange, D.G., and Sedmak, J., 1991, Japanese encephalitis virus (JEV): potentiation of lethality in mice by microwave radiation, *Bioelectromagnetics* 12:335-348.

Le, A.D., Poulos, C.K., and Cappell, H., 1979, Conditioned tolerance to the hypothermic effect of ethyl alcohol, *Science* 206:1109-1110.

Lebovitz, R.M., 1980, Behavioral changes during long-term microwave irradiation, *in*: "Proceeding of the International Symposium on the Biological Effects of Electromagnetic waves," UNSI, CNFRS, Jouy-en-Josas, France.

Lebovitz, R.M., and Seaman, R.L., 1977a, Microwave hearing: the responses of single auditory neurons in the cat to pulsed microwave radiation, *Radio Sci* 12(6):229-236.

Lebovitz, R.M., and Seaman, R.L., 1977b, Single auditory unit responses to weak, pulsed microwave radiation, *Brain Res* 126:370-375.

Levin, E.D., 1988, Psychopharmacological effects in the radial-arm maze, *Neurosci Biobehav Rev* 12:169-175.

Levinson, D.M., Grove, A.M., Clarke, L.R., and Justesen, D.R., 1982, Photic cuing of escape by rats from an intense microwave field, *Bioelectromagnetics* 3:105-116.

Liebman, P.A., Parker, K.R., and Dratz, E.A., 1987, The molecular mechanism of visual excitation and its relation to the structure and function of the rod outer segment, *Ann Rev Physiol* 49:765-791.

Lin, J.C., 1978, "Microwave Auditory Effects and Applications," Charles C. Thomas, Springfield, IL.

Lin, J.C. and Lin, M.F., 1980, Studies on microwaves and blood-brain barrier interaction, *Bioelectromagnetics* 1:313-323.

Lin, J.C. and Lin, M.F., 1982, Microwave hyperthermia-induced blood-brain barrier alterations, *Radiat Res* 89:77-87.

Lin-Liu, S., and Adey, W.R., 1982, Low frequency amplitude modulated microwave fields change calcium efflux rate from synaptosomes, *Bioelectromagnetics* 3:309-322.

Lippa, A.S., Klepner, C.A., Yunger, L., Sano, M.C., Smith, W.V., and Beer, B., 1978, Relationship between benzodiazepine receptors and experimental anxiety in rats, *Pharmac Biochem Behav* 9:853-856.

Lobanova, Ye. A., 1974a, Investigation on the susceptibility of animal to microwave irradiation following treatment with pharmacologic agents, *in*: "Biological Effects of Radiofrequency Electromagnetic Fields," Z.V. Gordon, ed., NTIS:JPRS 63321.

Lobanova, Ye. A., 1974b, The dependence of the temperature response to microwave irradiation and the initial functional state of the CNS, *in*: "Biological Effects of Radiofrequency Electromagnetic Fields," Z.V. Gordon, ed., NTIS:JPRS 63321.

Lovely, R.H., and Guy, A.W., 1975, Conditioned taste aversion in the rat induced by a single exposure to microwave, paper presented at the IMPI Microwave Power Symposium, University of Waterloo, Waterloo, Ontario, Canada.

Lovely, R.H., Myers, D.E., and Guy, A.W., 1977, Irradiation of rats by 918-MHz microwaves at 2.5 mW/cm^2: delineating the dose-response relationship, *Radio Sci* 12(6):139-146.

Lu, S.T., Lotz, W.G., and Michaelson, S.M., 1980, Advances in microwave-induced neuroendocrine effects: the concept of stress, *Proc IEEE* 68:73-77.

Lucchi, L., Moresco, R.M., Govoni, S., and Trabucchi, M., 1988, Effect of chronic ethanol treatment on dopamine receptor subtypes in rat striatum, *Brain Res* 449:347-351.

Mansour, A., Khachaturian, H., Lewis, M.E., Akil, H., and Watson, S.J., 1987, Autoradiographic differentiation of mu, delta, and kappa opioid receptors in the rat forebrain, *J Neurosci* 7:2445-2464.

Mackintosh, N.J., 1974, "The Psychology of Animal Learning," Academic Press, New York, NY.

Marr, M.J., de Lorge, J.O., Olsen, R.G., and Stanford, M., 1988, Microwaves as reinforcing events in a cold environment, *in*: "Electromagnetic Fields and Neurobehavioral Functions," M.E. O'Connor and R.H. Lovely, eds., *Prog Clin Biol Res* 257:219-234.

McAfee, R.D., 1961, Neurological effect of 3 cm microwave radiation, *Am J Physiol* 200: 192-199.

McAfee, R.D., 1963, Physiological effects of thermode and microwave stimulation of peripheral nerves, *Am J Physiol* 203: 374-380.

McKee., A., Dorsey, C.H., Eisenbrandt, D.L., and Woden, 1980, Ultrastructural observations of microwave-induced morphologic changes in the central nervous system of hamster, *Bioelectromagnetics* 1:206.

McRee, D.J., and Davis, H.G., 1984, Whole-body and local dosimetry on rats exposed to 2.45-GHz microwave radiation, *Health Phys* 46:315-320.

Medina, J.H., Novas, M.L., and DeRobertis, E., 1983a, Changes in benzodiazepine receptors by acute stress: different effects of chronic diazepam on R015-1788 treatment, *Eur J Pharmacol* 96:181-185.

Medina, J.H., Novas, M.L., Wolfman, C.N.V., Levi DeStein, M., and DeRobertis, E., 1983b, Benzodiazepine receptors in rat cerebral cortex and hippocampus undergo rapid and reversible changes after acute stress, *Neurosci* 9:331-335.

Merritt, J.H., Hartzell, R.H., and Frazer, J.W., 1976, The effect of 1.6 GHz radiation on neurotransmitters in discrete areas of the rat brain, *in*: "Biological Effects of Electromagnetic Waves," vol. 1, C.C. Johnson and M.C. Shore, eds., HEW Publication (FDA) 77-8010, Rockville, MD.

Merritt, J.H., Chamness, A.F., Hartzell, R.H., and Allan, S.J., 1977, Orientation effect on microwave-induced hyperthermia and neurochemical correlates, *J Microwave Power* 12:167-172.

Merritt, J.H., Chamness, A.F., and Allens, S.J., 1978, Studies on blood-brain barrier permeability after microwave radiation, *Radiat Environ Biophys* 15:367-377.

Merritt, J.H., Shelton, W.W., and Chamness, A.F., 1982, Attempts to alter $^{45}Ca^{2+}$ binding to brain tissue with pulse-modulated microwave energy, *Bioelectromagnetics* 3:475-478.

Michaelson, S.M. and Lin, J.C., 1987, "Biological Effects and Health Implications of Radiofrequency Radiation," Plenum Press, New York, NY.

Michaelson, S.M., Thomson, R.A.E., and Howland, J.W., 1961, Physiological aspects of microwave irradiation of mammals, *Am J Physiol* 201:351-356.

Miller, D.B., Christopher, J.P., Hunter, J., and Yeandle, S.S., 1984, The effect of exposure of acetylcholinesterase to 2450 MHz microwave radiation, *Bioelectromagnetics* 5:165-172.

Mitchell, C.L., McRee, D.J., Peterson, N.J., and Tilson, H.A., 1988, Some behavioral effects of short-term exposure of rats to 2.45-GHz microwave radiation, *Bioelectromagnetics* 9:259-268.

Mitchell, D.S., Switzer, W.G., and Bronaugh, E.L., 1977, Hyperactivity and disruption of operant behavior in rats after multiple exposure to microwave radiation, *Radio Sci* 12(6):263-271.

Mizukawa, K., Takayama, H., Sato, H., Ota, J., Haba, K., and Ogawa, N., 1989, Alterations of muscarinic cholinergic receptors in the hippocampal formation of stressed rat: in vitro quantitative autoradiographic analysis, *Brain Res* 478:187-192.

Modak, A.T., Stavinoha, W.B., and Dean, U.P., 1981, Effect of short electromagnetic pulses on brain acetylcholine content and spontaneous motor activity in mice, *Bioelectromagnetics* 2:89-92.

Moe, K.E., Lovely, R.H., Meyers D.E., and Guy, A.W., 1976, Physiological and behavioral effects of chronic low-level microwave radiation in rats, *in*: "Biological Effects of Electromagnetic Waves," vol. 1, C.C. Johnson and M.L. Shore, eds., HEW Publication (FDA) 77-8010, Rockville, MD.

Mohler, H., and Okada, T., 1977, Benzodiazepine receptor: demonstration in the central nervous system, *Science* 198:849-851.

Monahan, J.C., 1988, Microwave-drug interactions in the cholinergic nervous system of the mouse, *in*: "Electromagnetic Fields and Neurobehavioral Function," M.E. O'Connor and D.H. Lovely, eds., *Prog Clin Biol Res* 257:309-326.

Monahan, J.C., and Henton, W., 1977a, Microwave absorption and taste aversion as a function of 915 MHz radiation, *in*: "Symposium on Biological Effects and Measurement of Radio Frequency Microwaves," D.J. Hazzard, ed., HEW Publication (FDA) 77-8026, Rockville, MD.

Monahan, J.C., and Henton, W., 1977b, Free-operant avoidance and escape from microwave radiation, *in*: "Symposium on Biological Effects and Measurement of Radio Frequency Microwaves," D.J. Hazzard, ed., HEW Publication (FDA) 77-8026, Rockville, MD.

Monahan, J.C., and Henton, W., 1979, The effect of psychoactive drugs on operant behavior induced by microwave radiation, *Radio Sci* 14(6):233-238.

Monahan, J.C., and Ho, H., 1976, Microwave-induced avoidance behavior in the mouse, *in*: "Biological Effects of Electromagnetic Waves, Selected Papers of the USNC/URSI Annual Meeting," vol . 1, C.C. Johnson and M.L. Shore , eds., HEW Publication (FDA) 77-8010, Rockville, MD.

Mowrer, W.H., 1939, A stimulus-response analysis of anxiety and its role as a reinforcing agent, *Pychol Rev* 46:553-565.

Muller, P., Britton, R.S., and Seeman, P., 1980, The effect of long-term ethanol on brain receptors for dopamine, acetylcholine, seratonin and noradrenaline, *Eur J Pharmacol* 65:31-37.

Neilly, J.P. and Lin, J.C., 1986, Interaction of ethanol and microwaves on the blood-brain barrier of rats, *Bioelectromagnetics* 7:405-414.

Neubauer, C., Phelan, A.M., Kues, H., and Lange, D.G., 1990, Microwave irradiation of rats at 2.45 GHz activates pinocytotic-like uptake of tracer by capillary endothelial cells of cerebral cortex, *Bioelectromagnetics* 11:261-268.

Nichols, M.L., Hubbell, C.L., Kalsher, M.J., and Reid, L.D., 1991, Morphine increases intake of beer among rats, *Alcohol* 8:237-240.

O'Connor, M.E., 1988, Prenatal microwave exposure and behavior, *in*: "Electromagnetic Fields and Neurobehavioral Function," M.E. O'Connor and R.H. Lovely, eds., *Prog Clin Biol Res* 257:265-288.

Oscar, K.J. and Hawkins, T.D., 1977, Microwave alteration of the blood-brain barrier system of rats, *Brain Res* 126:281-293.

Oscar, K.J., Gruenace, S.P., Folker, M.T., and Rapoport S.L., 1981, Local cerebral blood flow after microwave exposure, *Brain Res* 204:220-225.

Overstreet, D.H., and Yamamura, H., 1979, Receptor alteration and drug tolerance, *Life Sci* 25:1865-1878.

Panksepp, J., Zolovick, A.J., Jalowiec, J.E., Stern, W.C., and Morgane, P.J., 1973, Fenfluramine: effects on aggression, *Biol Psychiat* 6:181-186.

Pappas, B.A., Anisman, H., Ings, R., and Hill, D.A., 1983, Acute exposure to pulsed microwaves affects

neither pentylenetetrazol seizures in the rat nor cholordiazepoxide protection against such seizures, *Radiat Res* 96:486-496.

Pickard, W.F., and Barsoum, Y.M., 1981, Radiofrequency bioeffects at the membrane level: separation of thermal and athermal contributions in the Characeae, *J Membrane Biol* 61:39-54.

Plotnikoff, N., Murgo, A., Faith, R., and Wybran, J., eds., 1991, "Stress and Immunity," CRC Press, Boca Raton, FL.

Polc, P., 1988, Electrophysiology of benzodiazepine receptor ligands: multiple mechanisms and sites of action, *Prog Neurobiol* 31:349-424.

Preston, E., and Prefontaine, G., 1980, Cerebrovascular permeability to sucrose in the rat exposed to 2450-MHz microwaves, *J Appl Physiol* 49:218-223.

Preston, E., Vavasour, E.J., and Assenheim, H.M., 1979, Permeability of the blood-brain barrier to mannitol in the rat following 2450 MHz microwave irradiation, *Brain Res* 174:109-117.

Price, D.L., Cork, L.C., Struble, R.G., Whitehouse, P.J., Kitt, C.A., and Walker, L.C., 1985, The functional organization of the basal forebrain cholinergic systems in primates and the role of the system in Alzheimer's disease, *Ann N Y Acad Sci* 444:287-295.

Quock, R.M., Fujimoto, J.M., Ishii, T.K., and Lange, D.G., 1986a, Microwave facilitation of methylatropine antagonism of central cholinomimetic drug effects, *Radiat Res* 105:328-340.

Quock, R.M., Konchich, F.J., Ishii, T.K. and Lange, D.G., 1986b, Microwave facilitation of methylatrophine antagonism of morphine-induced analgesic in mice, *J Bioelectricity* 5:35-46.

Quock, R.M., Konchich, F.J., Ishii, T.K., and Lange, D.G., 1987, Microwave facilitation of domperidone antagonism of apomorphine-induced stereotypic climbing in mice, *Bioelectromagnetics* 8:45-55.

Quock, R.M., Bixby, R.R., Klauenberg, B.J., and Merritt, J.H., 1990, Influence of microwave exposure on chlordiazepoxide effects in the mouse staircase test, *Abst Ann Meeting Bioelectromagnetics Soc* 12:92.

Reid, L.D., Delconte, J.D., Nichols, M.L., Bilsky, E.J., and Hubbell, C.L., 1991, Tests of opioid deficiency hypothesis of alcoholism, *Alcohol* 8:247-257.

Reynolds, G.S., 1968, "Primer of Operant Conditioning," Scott & Foreman, Glenview, IL.

Roberti, B., Heebels, G.H., Hendricx, J.C.M., deGreef, A.H.A.M., and Wolthuis, O.L., 1975, Preliminary investigation of the effect of low-level microwave radiation on spontaneous motor activity in rats, *Ann NY Acad Sci* 247:417-424.

Rudnev, M., Bokina, A., Eksler, N., and Navakatikyan, M., 1978, The use of evoked potential and behavioral measures in the assessment of environmental insult *in*: "Multidisciplinary Perspectives in Event-Related Brain Potential Research," D.A. Otto, ed., EPA-600/9-77-043, U.S. Environmental Protection Agency, Research Triangle Park, NC.

Sagan, P.M., and Medici, R.G., 1979, Behavior of chicks exposed to low-power 450-MHz fields sinusoidally modulated at EEG frequencies, *Radio Sci* 14(6):239-245.

Sanders, A.P., and Joines, W.T., 1984, The effects of hyperthermia and hyperthermia plus microwaves on rat brain energy metabolism, *Bioelectromagnetics* 5:63-70.

Sanders, A.P., Schaefer, D.J., and Joines, W.T., 1980, Microwave effects on energy metabolism of rat brain, *Bioelectromagnetics* 1:171-182.

Sanders, A.P., Joines, W.T., and Allis, J.W., 1984, The differential effect of 200, 591, and 2450 MHz radiation on rat brain energy metabolism, *Bioelectromagnetics* 5:419-433.

Sanders, A.P., Joines, W.T., and Allis, J.W., 1985, Effect of continuous-wave, pulsed, and sinusoidal-amplitude-modulated microwaves on brain energy metabolism, *Bioelectromagnetics* 6:89-97.

Sanza, J.N., and de Lorge, J., 1977, Fixed interval behavior and rats exposed to microwaves at low power densities, *Radio Sci* 12(6):273-277.

Scheich, H., Langner, G., Tidemann, C., Coles, R.B., and Guppy, A., 1986, Electro-reception and electrolocation in platypus, *Nature* 319:401-402.

Scholl, D.M., and Allen, S.J., 1979, Skilled visual-motor performance by monkeys in a 1.2-GHz microwave field, *Radio Sci* 14(6): 247-252.

Schrot, J., Thomas, J.R., and Banvard, R.A., 1980, Modification of the repeated acquisition of response sequences in rats by low-level microwave exposure, *Bioelectromagnetics* 1:89-99.

Schwan, H.P., 1971, Interaction of microwave and radiofrequency radiation with biological systems, *IEEE Microwave Th Tech* MTT-19:146-150.

Schwan, H.P., 1977, Electrical membrane potentials, tissue excitation, and various relevant interpretations, *in*: "Biologic Effects of Electric and Magnetic Fields Associated with Proposed Project Seafarer," National Academy of Sciences, Washington, DC.

Seaman, R.L., and Lebovitz, R.M., 1987, Auditory unit responses to single pulse and twin-pulse microwave stimuli, *Hearing Res* 26:105-116.

Seaman, R.L., and Lebovitz, R.M., 1989, Thresholds of cat cochlea nucleus neurons to microwave pulses, *Bioelectromagnetics* 10:147-160.

Seaman, R.L., and Wachtel, H., 1978, Slow and rapid responses to CW and pulsed microwave radiation by individual Aplysia pacemakers, *J Microwave Power* 13:77-86.

Servantie, B., Batharion, G., Joly, R., Servantie, A.M., Etienne, J., Dreyfus, P., and Escoubet, P., 1974, Pharmacologic effects of a pulsed microwave field, *in*: "Biological Effects and Health Hazards of Microwave Radiation: Proceedings of an International Symposium," P. Czerski, et al., eds., Polish Medical Publishers, Warsaw.

Servantie, B., Servantie, A.M., and Etienne, J., 1975, Synchronization of cortical neurons by a pulsed microwave field as evidenced by spectral analysis of electrocorticograms from the white rat, *Ann N Y Acad Sci* 247:82-86.

Shandala, M.G., Dumanski, U.D., Rudnev, M.I., Ershova, L.K., and Los, I.P., 1979, Study of nonionizing microwave radiation effects upon the central nervous system and behavior reaction, *Environ Health Perspect* 30:115-121.

Shelton, W.W., Jr., and Merritt, J.H., 1981, In vitro study of microwave effects on calcium efflux in rat brain tissue, *Bioelectromagnetics* 2:161-167.

Sheppard, A.R., Bawin, S.M., and Adey, W.R., 1979, Models of long-range order in cerebral macromolecules: effect of sub-ELF and of modulated VHF and UHF fields, *Radio Sci* 14:141-145.

Siegel, S., 1977, Morphine tolerance acquisition as an associative process, *J Comp Physiol Psychol* 3:1-13.

Siegel, S., Hinson, R.E., Krank, M.D., and McCully, J., 1982, Heroin "overdose" death: contribution of drug-associated environmental cues, *Science* 216:436-437.

Snyder, S.H., 1971, The effect of microwave irradiation on the turnover rate of serotonin and norepinephrine and the effect of microwave metabolizing enzymes, Final Report, Contract No. DADA 17-69-C-9144, U.S. Army Medical Research and Development Command, Washington, DC (NTLT AD-729 161).

Solomon, R.L., and Wynne, L.C., 1954, Traumatic avoidance learning: the principles of anxiety conservation and partial irreversibility, *Psychol Rev* 61:353-385.

Soubrie, P., Thiebot, M.H., Jobert, A., Montastruc, J.L., Hery, F., and Hamon, M., 1980, Decreased convulsant potency of picotoxin and pentetrazol and enhanced [^{3}H] flunitrazepam cortical binding following stressful manipulations in rat, *Brain Res* 189:505-519.

Stavinoha, W.B., Medina, M.A., Frazer, J., Weintraub, S.T., Ross, D.H., Modak, A.T., and Jones, D.J., 1976, The effects of 19 megacycle irradiation on mice and rats, *in*: "Biological Effects of Electromagnetic Waves," vol. 1, C.C. Johnson and M.L. Shore, eds., HEW Publication (FDA) 77-8010, Rockville, MD.

Steriade, M., and Biesold, D. eds., 1990, "Brain Cholinergic Systems," Oxford University Press, Oxford.

Stern, S., 1980, Behavioral effects of microwaves, *Neurobehav Toxicol* 2:49-58.

Stverak, I., Martha, K., and Pafkova, G., 1974, Some effects of various pulsed field on animals with audiogenic epilepsy, *in*: "Biological Effects and Health Hazards of Microwave Radiation: Proceedings of an International Symposium," P. Czerski, et al., eds., Polish Medical Publishers, Warsaw.

Stryer, L., 1987, The molecules of visual excitation, *Scientific American* 257(1):32-40.

Sutton, C.H., and Carroll, F.B., 1979, Effects of microwave-induced hyperthermia on the blood-brain barrier of the rat, *Radio Sci* 14:329-334.

Switzer, W.G., and Mitchell, D.S., 1977, Long-term effects of 2.45 GHz radiation on the ultrastructure of the cerebral cortex and hematologic profiles of rats, *Radio Sci* 12:287-293.

Syvalahti, E.K.G., Hietala, J., Roytta, M., and Gronroos, J., 1988, Decrease in the number of rat brain dopamine and muscarinic receptors after chronic alcohol intake, *Pharmacol Toxicol* 62:210-212.

Tabakoff, B., and Hoffman, P.L., 1979, Development of functional dependence on ethanol in dopaminergic systems, *J Pharmacol Exp Ther* 208:216-222.

Takashima, S., Onaral, B., and Schwan, H.P., 1979, Effects of modulated RF energy on the EEG of mammalian brain, *Rad Environ Biophys* 16:15-27.

Taylor, E.M., and Ashleman, B.T., 1974, Analysis of central nervous system involvement in the microwave auditory effect, *Brain Res* 74:201-208.

Taylor, E.M., and Ashleman, B.T., 1975, Some effects of electromagnetic radiation on the brain and spinal cord of cats, *Ann NY Acad Sci* 247:63-73.

Thomas, J.R., and Maitland, G., 1979, Microwave radiation and dextroamphetamine: evidence of combined effects on behavior of rats, *Radio Sci* 14(6):253-258.

Thomas, J.R., Finch, E.D., Fulk, D.W., and Burch, L.S., 1975, Effects of low level microwave radiation on behavioral baselines, *Ann NY Acad Sci* 247:425-432.

Thomas, J.R., Yeandle, S.S., and Burch, L.S., 1976, Modification of internal discriminative stimulus control of behavior by low levels of pulsed microwave radiation, *in*: "Biological Effects of Electromagnetic Waves," vol. 1, C.C. Johnson and M.L.Shore, eds., HEW Publication (FDA) 77-8010, Rockville, MD.

Thomas, J.R., Burch, L.S., and Yeandle, S.C., 1979, Microwave radiation and chlordiazepoxide: synergistic effects on fixed interval behavior, *Science* 203:1357-1358.

Thomas, J.R., Schrot, J., and Banvard, R.A., 1980, Behavioral effects of chlorpromazine and diazepam combined with low level microwaves, *Neurobiol* 2:131-135.

Tolgskaya, M.S., and Gordon, Z.V., 1973, Pathological effects of radiowaves, (Translated from Russian by B. Haigh), Consultants Bureau, New York, NY.

Wachtel, H., Seaman, R., and Joines, W., 1975, Effects of low-intensity microwaves on isolated neurons, *Ann NY Acad Sci* 247:46-62.

Wangemann, R.T., and Cleary, S.F., 1976, The in vivo effects of 2.45-GHz microwave radiation on rabbit serum components and sleeping times, *Radiat Environ Biophys* 13:89-103.

Ward, T.R., Elder, J.A., Long, M.D., and Svendsgaard, D., 1982, Measurement of blood-brain barrier permeation in rats during exposure to 2450-MHz microwaves, *Bioelectromagnetics* 3:371-383.

Ward, T.R., and Ali, J.S., 1985, Blood-brain barrier permeation in the rat during exposure to low-power 1.7-GHz microwave radiation, *Bioelectromagnetics* 2:131-143.

Ward, T.R., Svensgaard, D.J., Spiegel, R.J., Puckett, E.T., Long, M.D., and Kinn, J.B., 1986, Brain temperature measurements in rats: a comparison of microwave and ambient temperature exposures, *Bioelectromagnetics* 7:243-258.

Weizman, R., Weizman, A., Kook, K.A., Vocci, F., Deutsch, S.I., and Paul, S.M., 1989, Repeated swim stress alters brain benzodiazepine receptors measured in vivo, *J Pharmacol Exp Ther* 249:701-707.

Wild, K.D., and Reid, L.D., 1990, Modulation of ethanol-intake by morphine: evidence for a central site of action, *Life Sci* 47:PL-49-PL-54.

Williams, W.M., Hoss, W., Formaniak, M., and Michaelson, S.M., 1984a, Effect of 2450 MHz microwave energy on the blood-brain barrier to hydrophilic molecules, A. Effect on the permeability to sodium fluorescein, *Brain Res Rev* 7:165-170.

Williams, W.M., del Cerro, M., and Michaelson, S.M., 1984b, Effect of 2450 MHz microwave energy on the blood-brain barrier to hydrophilic molecules, B. Effect on the permeability to HRP, *Brain Res Rev* 7: 171-181.

Williams, W.M., Platner, J., and Michaelson, S.M., 1984c, Effect of 2450 MHz microwave energy on the blood-brain barrier to hydrophilic molecules, C. Effect on the permeability to ^{14}C-sucrose, *Brain Res Rev* 7:183-190.

Williams, W.M., Lu, S.-T., del Cerro, M., and Michaelson, S.M., 1984d, Effect of 2450 MHz microwave energy on the blood-brain barrier to hydrophilic molecules, D. Brain temperature and blood-brain barrier permeability to hydrophilic tracers, *Brain Res Rev* 7:191-212.

Wikler, A., 1973a, Dynamics of drug dependence: Implications of a conditioning theory for research and treatment, *Arch Gen Psychiat* 28:611-616.

Wikler, A., 1973b, Conditioning of successive adaptive responses to the initial effects of drugs, *Conditioned Reflex* 8:193-210.

Wilson, B.A., Zook, J.M., Joines, W.T., and Casseday, J.H., 1980, Alterations in activity at auditory nuclei of the rat induced by exposure to microwave radiation: autoradiographic evidence using [^{14}C]-2-deoxy-D-glucose, *Brain Res* 187:291-306.

Woods, S.C., Makous, W., and Hutton, R.A., 1969, Temporal parameters of conditioned hypoglycemia, *J Comp Physiol Psychol* 69:301-307.

Young, W., 1980, The effect of microwaves (9.7 GHz) on membrane bound acetylcholinesterase in the vagal heart system, *Fed Proc* 39:410.

Zeman, G.H., Chaput, R.L., Glazer, Z.R., and Gershman, L.L., 1973, Gamma-aminobutyric acid metabolism in rats following microwave exposure. *J Microwave Power* 8:213-216.