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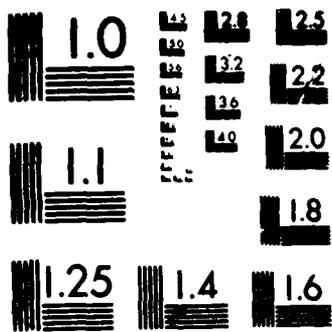
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**AFFERENT MECHANISMS OF MICROWAVE-INDUCED BIOLOGICAL EFFECTS**

H. Lai, A. Horita, C. K. Chou, and A. W. Guy

**Bioelectromagnetics Research Laboratory  
Center for Bioengineering  
College of Engineering  
University of Washington School of Medicine  
Seattle, Washington**

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## AFFERENT MECHANISMS OF MICROWAVE-INDUCED BIOLOGICAL EFFECTS

This is a summary of the research supported by the Office of Naval Research, done in our laboratories during the past seven years. The research concerns the effects of low-level microwave irradiation on neurological functions in the rat. Details of the experimental results have been reported in the following publications:

- (a) Lai H, Horita A, Chou CK, Guy AW (1983): Psychoactive drug response is affected by acute low-level microwave radiation. Bioelectromagnetics 4:205-214.
- (b) Lai H, Horita A, Chou CK, Guy AW (1984a): Effects of acute low-level microwaves on pentobarbital-induced hypothermia depend on exposure orientation. Bioelectromagnetics 5:203-211.
- (c) Lai H, Horita A, Chou CK, Guy AW (1984b): Ethanol-induced hypothermia and ethanol consumption in the rat are affected by low-level microwave irradiation. Bioelectromagnetics 5:213-220.
- (d) Lai H, Horita A, Chou CK, Guy AW (1984c): Microwave-induced postexposure hyperthermia: Involvement of endogenous opioids and serotonin. IEEE Trans Microwave Theory Tech MTT-32:882-887.

- (e) Chou CK, Guy AW, McDougall JA, Lai H (1985): Specific absorption rate in rats exposed to 2450-MHz microwaves under seven exposure conditions. Bioelectromagnetics 6:73-88.
- (f) Lai H, Horita A, Chou CK, Guy AW (1986a): Effects of low-level microwave irradiation on amphetamine hyperthermia are blockable by naloxone and classically conditionable. Psychopharmacology 88:354-361.
- (g) Lai H, Horita A, Chou CK, Guy AW (1986b): Low-level microwave irradiation attenuates naloxone-induced withdrawal syndrome in morphine-dependent rats. Pharmac Biochem Behav 24:151-153.
- (h) Lai H, Horita A, Chou CK, Guy AW (1986c): Naloxone-blockable, classically conditionable hyperthermia in the rat after microwave exposure. In Cooper K, Lomax P, Schonbaum E and Veale WL (eds): Homeostasis and Thermal Stress: Experimental and Therapeutic Advances. Basel: Karger Press, pp 174-179.
- (i) Lai H, Horita A, Chou CK, Guy AW (1987a): Low-level microwave irradiations affect central cholinergic activity in the rat. J Neurochem 48:40-45.
- (j) Lai H, Horita A, Chou CK, Guy AW (1987b): Effects of low-level microwave irradiation on hippocampal and frontal cortical choline uptake are classically conditionable. Pharmac Biochem Behav (In press, August 1987).

In addition, we have also published the following review paper:

Lai H, Horita A, Chou CK, Guy AW (1987c): A review of microwave irradiation and actions of psychoactive drugs. IEEE Eng Med Bio 6(1):31-36.

A paper entitled "Acute microwave exposure and central cholinergic activity: Study on the parameters of irradiation," to be submitted to Bioelectromagnetics, is in preparation.

Our data point to the following general conclusions:

- (1) Acute exposure to microwaves (45 minutes, at power density  $1 \text{ mW/cm}^2$  with whole body SAR of  $0.6 \text{ W/kg}$ , pulsed or continuous wave) causes a variety of neurological effects. These include: interaction with psychoactive drugs and changes in cholinergic activity in the central nervous system.
- (2) After repeated exposure, the effects of microwaves are classically conditionable to cues in the exposure environment.
- (3) Endogenous opioids apparently play an important mediating role in these effects of microwaves, and microwaves and "stressors" have similar effects.

In the following sections, each of the above conclusions has been briefly discussed.

## (1) Neurological Effects of Acute Microwave Exposure

In our first series of experiments, we investigated the effects of acute microwave exposure on the actions of a variety of psychoactive drugs. In these experiments, rats were exposed in the cylindrical waveguide system of Guy et al (Radio Sci 14:63-74, 1979) with 2450-MHz pulsed (2  $\mu$ s, 500 pps) microwaves for 45 minutes. The power density averaged over the waveguide cross section used in the experiments was 1 mW/cm<sup>2</sup> (average whole body SAR 0.6 W/kg). Drug effects were tested immediately after exposure. We found (Lai et al, 1983; 1984a, b) that the following drug actions were altered in the irradiated animals: apomorphine-hypothermia, apomorphine-stereotypic behavior, amphetamine-hyperthermia, morphine-catalepsy, pentobarbital-hypothermia, pentobarbital-narcosis, ethanol-hypothermia, and ethanol consumption. Since some of the above drug actions were attenuated whereas others were potentiated by microwave exposure, and these drugs can readily pass through the blood-brain-barrier and reach the sites of action in the brain, we concluded that the effects of microwaves on these drug actions were not due to changes in the permeability of the blood-brain-barrier. However, we cannot rule out the possibility that microwave changes the local distribution of the drugs in the brain. Another interesting finding is that exposure of rats in two different orientations in the cylindrical waveguide (facing towards or away from the source) had different effects on the pentobarbital-induced hypothermia (Lai et al, 1984a). In the exposure system, the average whole body SARs are similar in the two orientations of exposure, whereas localized absorption patterns are different (Chou et al, Bioelectromagnetics 6:73-88, 1985).

These data suggest that localized SARs are important considerations in determining the effects of microwaves.

In another series of more recent experiments, we measured sodium-dependent high-affinity choline uptake, an index of cholinergic activity in neural tissue, in four regions of the brain after acute microwave exposure. We found that after 45 minutes of exposure, choline uptake activity in the hippocampus and frontal cortex was decreased, whereas no significant effect was found in the hypothalamus and striatum (Lai et al, 1987a).

The effects of varying the different parameters of microwave radiation on central choline uptake were then investigated. Rats were irradiated in the cylindrical waveguide for 20 minutes instead of 45 minutes. Measurement of choline uptake showed that uptake activity was enhanced in the hippocampus, frontal cortex, and hypothalamus, whereas no significant effect was observed in the striatum. Thus, central cholinergic activity was increased after a short period (20 min) of microwave exposure, whereas a decrease in activity was observed after a larger period (45 min) of exposure. This supports the previous reports by others that the cholinergic system gives biphasic response to stimuli (Gilad et al, Brain Res 267:171-174, 1983; Finkelstein et al, Brain Res 345:314-317, 1985; Lai, Pharmac Biochem Behav, 1987 in press).

In further experiments, rats were irradiated with continuous-wave or pulsed 2450-MHz microwaves in cylindrical waveguides or the miniature anechoic chambers (Guy, J Microwave Power 14:327-336, 1979). The average whole body SAR was kept at 0.6 W/kg for all exposure conditions.

Sodium-dependent high-affinity choline uptake was determined in the hippocampus, frontal cortex, hypothalamus and striatum immediately after 45 minutes of exposure. Frontal cortical choline uptake was decreased under all irradiation conditions. Hippocampal choline uptake was decreased in animals after exposure to pulsed microwaves, but no significant effect was seen after continuous-wave microwave exposure. Striatal choline uptake was decreased after microwave exposure in the miniature anechoic chamber, but no significant effect was seen after exposure in the cylindrical waveguide. Microwaves did not significantly affect hypothalamic cholinergic activity under all irradiation studied.

Taken together, these data indicate the complex nature of the effect of microwaves on neurological functions. Duration of exposure, whether the radiation is pulsed or continuous, and probably local distributions of the absorbed energy in the body and/or the brain must be taken into consideration.

## (2) The Effects of Microwaves are Classically Conditionable to Cues in the Exposure Environment

A series of experiments was performed to investigate the biological effects of repeated exposure to low-level microwaves. Particularly, the development of tolerance and classical conditioning of the effects were studied. If tolerance develops, the effects of microwaves should diminish after repeated exposure. In classical conditioning, neutral stimuli are paired with unconditional stimulus. After repeated pairing, the previously neutral stimulus, when presented alone, will be able to elicit a response.

In our case, the microwaves are the unconditional stimuli and cues in the exposure environment served as the conditioned (neutral) stimulus. After repeated exposure of rats to microwaves in the waveguide, a subsequent session of sham-exposure, i. e., put in the waveguide without the microwaves turned on, will elicit a response (a conditioned response). In the literature, it has been shown that the conditioned response can be similar or opposite to the unconditioned response.

So far, several effects of microwaves have been studied and they have been found to be classically conditionable to environmental cues. These include the microwave-induced effects in amphetamine-hyperthermia (Lai et al, 1986a); ethanol-hypothermia (Lai et al, Abst Soc Neuroscience 11:570, 1984); postexposure-hyperthermia (Lai et al, 1986c); and sodium-dependent high-affinity choline uptake in the frontal cortex and hippocampus (Lai et al, 1987b). Furthermore, it is interesting that conditioned effects both similar and opposite to the unconditioned effects were obtained depending on the response studied. Explanation for these effects requires further understanding of the neural mechanisms affected by microwave irradiation.

Development of tolerance to the effects of microwaves was observed in several microwave-induced effects (ethanol-hypothermia and hippocampal choline uptake). However, in several incidences, no tolerance was seen at least after 10-15 sessions of 45 minute exposures (amphetamine-hyperthermia, postexposure hyperthermia, and frontal cortical choline uptake). Perhaps, more extensive exposure is required to develop tolerance to the latter responses.

The development of tolerance and classical conditioning of the effects of low-level microwaves may have important consequences in an animal's response and coping to repeated exposure. These effects are especially relevant in occupational situations where repeated exposure to microwave irradiation is unavoidable.

### (3) Involvement of Endogenous Opioids in the Effects of Microwaves

Data from our experiments also indicate that some of the neurological effects of low-level microwave exposure are mediated by endogenous opioids. Blockade of an effect by treatment with low doses of narcotic antagonist (naloxone or naltrexone) was used as a criterion for the involvement of endogenous opioids. Data from our experiments supporting the role played by endogenous opioids on the biological effects of microwaves, can be summarized as follows: (a) microwave irradiation enhanced morphine-induced catalepsy in the rat (Lai et al, 1983); (b) microwave exposure attenuated the naloxone-induced wet-dog shake, a morphine withdrawal symptom in morphine-dependent rats (Lai et al, 1986b); (c) acute microwave irradiation caused a transient increase in body temperature immediately after exposure, and this effect was blocked by pretreatment with narcotic antagonist (Lai et al, 1984c); (d) the effects of microwaves on ethanol-hypothermia, amphetamine-hyperthermia, and apomorphine-hypothermia were blocked by naloxone (Lai et al, 1986a, and unpublished results), and (e) acute microwave irradiation-induced changes in cholinergic activity in the brain were blocked by pretreatment with narcotic antagonist.

In the above cases, pretreatment with narcotic antagonist had no significant effect on the responses of the sham-irradiated animals (compared with those of saline-treated animals). These data lead us to propose the following hypothesis: "Low-level microwave irradiation activates endogenous opioids in the nervous system. Activation of these endogenous opioids, in turn, influences an animal's response to psychoactive drugs and trigger the neurochemical and physiological responses."

In our review paper (Lai et al, 1987c), we compared the effects of microwave irradiation and those of "stressors" on drug actions and neurological functions. The patterns are similar. This suggests that stress may be a mediating factor in eliciting the neurological effects of microwaves. This hypothesis also compliments the above hypothesis that microwave radiation activates endogenous opioids, since endogenous opioids are involved in an animal's response to "stressors" (Amir et al, Neurosci Biobehav Rev 4:77-80, 1980).

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