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Physiological Responses Evoked in Mice by High Power Microwave Pulses

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The investigator's primary objective was to determine whether bursts of narrow pulse width, high intensity microwaves of low average power, would have different effects on the brain than would CW exposures yielding equivalent average SAR values. Two rather different approaches for ascertaining the neurophysiological response to patterned(pulsed)microwaves were followed. In one experiment, mice were exposed to single bursts of pulsed microwaves with sufficient energy to produce clear after effects, reduced activity, or "hypokinesis." In the other experiment, each mouse was exposed sequentially to various microwave pulse bursts or CW radiation of substantially less energy, and the threshold for "evoking" motor response(body movements)is ascertained.

Neurological Deficits or "Hypokinesis--"It had previously been demonstrated that mice and other animals exposed to thermally stressful levels of microwave energy would display neurological symptoms such as reduced activity(hypokinesis), partial paralysis, seizures. We wished to determine whether such effects

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FOREWORD

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Howard [illegible] 2/26/88
PI Signature Date

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Evoked Reflexive Movements:

Statement of Problem

The use of microwave apparatus in military and other applications is progressively involving higher peak pulse powers and narrower pulse widths. However, much of what is understood concerning the bioeffects of microwave exposure is based on studies of continuous wave (CW), or relatively low peak power, longer duration pulses. Difficulty arises with protecting those potentially exposed to high peak power pulsed microwave energy. The applicability of current (CW) safety standards have not been determined. There is therefore a pressing need to extend research to situations involving the use of narrow microwave pulses having extremely high peak powers.

The primary objective of this project was to determine whether bursts of narrow intense microwave pulses, of low average power (i.e., very high peak to average power ratio), would have substantially different effects on the brain than would CW exposures, yielding equivalent average SAR values. Two rather different strategies for ascertaining the neurophysiological response to patterned (pulsed) microwave can be followed. In one experiment mice are exposed to a single burst of pulsed microwaves with sufficient energy to produce clear aftereffects or "hypokinesis". These effects produce reduced activity and other neurological deficits. In the other experiment, each mouse is exposed sequentially to various microwave pulse bursts or CW radiation of substantially less energy, and the threshold for "evoking" motor responses (body movements) are ascertained. A prerequisite to the studies was the development of an exposure system for delivering the microwave energy predominately to the head (brain) of the mouse. Further details as to methodology, results and interpretation of these two approaches follows.

Background

Formulation of safety standards have, for the most part, been based on the time averaged power of pulsed microwave radiation.(1) This implies that it is the thermal content of the pulse trains over relatively long times (i.e., many seconds or minutes) that is the salient factor. Average power is a reliable indicator of the "bulk" temperature rises that would be induced in animal (or human) bodies over these longer times, but it is likely that such temperature rises are not the most significant determinants of a bioeffect.(2) There are several example cases in which microwave pulses are distinctly more effective in eliciting a physiological response than CW microwave exposures yielding the same "bulk" thermal endpoints. Perhaps the best understood of these phenomena is that of "microwave hearing," in which narrow microwave pulses (a few microseconds) selectively lead to thermoelastically based acoustic waves which are perceived as "clicks."(3) In a previous study (Wachtel et. al., 1984), we showed that single brief exposures (0.2 to 2 seconds) to intense CW microwaves lead to stressful temperature rises (2^oC to 8^oC) that are usually accompanied by neurological deficits that far outlast the exposure period and were often irreversible. Such deficits included reduced spontaneous activity (hypokinesis), aberrant movement patterns, partial paralysis, or seizures. These effects appear to be due to actual damage to neural elements even though such damage is sometimes reversible. The preponderance of evidence suggests that such damages are due to the associated thermal stresses.(4)

The other category of neural responses to microwave absorption is of a perturbing, rather than a damaging nature, and it is generally associated with much smaller brain temperature rises (less than 1^oC). For example, bursts of high peak power pulses having low average power content can produce auditory sensations, cause changes in electroencephalographic (EEG) patterns and modulate firing activity in isolated neurons. In an earlier study (Wachtel, et. al., 1984), we had reported that brief CW microwave exposures (0.01 to 0.1 seconds) could evoke heart and respiratory rate changes in mice. These reflexive motions were not mimicked by exposures to the same total CW energy delivered over longer time intervals (several seconds). This observation raised the possibility that these types of reflex responses might be more selectively evoked by narrow pulses (10 usec) having high peak power but low average power. The microwave exposure facilities at the Walter Reed Army Institute of Research were made available to us for the purposes of testing this general hypothesis and assessing the degree to which such pulses might pose a hazard for exposed personnel.

Experimental Methods and Results

The source of both pulsed and CW microwave energy was a modified Cober Transmitter capable of delivering 1 MW peak power at 1250 MHz. This system fed a custom designed resonant waveguide cavity into the end of which the head of the subject mouse was placed. To avoid the difficulties of coupling energy into moving animals, each mouse was constrained within the modified cylinder of a 60 cc syringe. Details of this exposure system (See Figure 1) and the dosimetric techniques used have been reported by Bassen, et.al., 1988. Under optimum circumstances peak pulse SARs of 20 Megawatts/kg can be produced in the center of a mouse brain using this system with a minimal RF absorption occurring in other parts of the body. To our knowledge, this figure exceeds any other reported values for peak pulse tissue SARs generated in vivo.

1. Experimental Animals: BALB-C mice ranging in weight from 13 to 27 grams were selected for this study because their small head size enabled us to induce extremely high peak pulse powers (up to 20 megawatts/kg) in the midbrain region. The BALB-C species also was tolerant of the mechanical constraint that it was necessary

to endure in these experiments. Constrained BALB-C mice became quiescent within a few minutes, and were amenable to the monitoring of body movements specifically evoked by microwave pulse bursts. Experimental animals were housedinenvironmentally controlled cage rooms and the quality of their care was consistent with, or in excess of, NIH guidelines.

2. Exposure Procedures: Each mouse to be exposed and tested was placed within the cylindrical (modified 60 cc syringe) constraint for 20 minutes, which proved sufficient to attain a quiescent state in which only occasional spontaneous movements were seen. The degree of confinement imposed on the mouse was sufficient to keep its head in a stable position without unduly affecting respiratory movements. In an earlier study, (Pulford, et al., 1987) mice had been found to be quite tolerant of such confinement, enduring eight hours or more. In the present study, however, each experiment was completed in 20 minutes or less.

3. Neurological Deficit (Hypokinesis) Measurements: It had previously been demonstrated that mice and other animals exposed to thermally stressful levels of microwave energy would display neurological symptoms such as reduced activity (hypokinesis), partial paralysis, and seizures. We wished to determine whether such effects would be apparent at lower energy levels if brief, high peak power (microsecond) pulses rather than CW or wider (millisecond) pulses were utilized. To explore this question, BALB-C mice (weighing from 18-27 g) were exposed within a waveguide system capable of delivering peak pulse SARs up to 20 megawatts/kg (at 1250 MHz). Each post-exposure mouse, including sham exposures, was immediately monitored for 5 to 10 minutes in a Harvard Instruments standard activity cage. With it's degrees of movement recorded as a rate, the animal's activity was also recorded as images on video tape. Assessments of neurological deficits (hypokinesis) were based on activity counts as well as interpretations of the video recordings. Initial analysis of these data indicate that delivery of 32 to 64 pulses of ten microseconds (at a range of 80 or 160 pps), with a temporal peak SAR of 20 MW/kg would yield a variety of moderate, reversible, neurological deficits while 128 pulses would usually result in severe impairment or death. When the same total energy was delivered over a similar time period using less intense or shorter duration pulses, similar effects were seen. Exposure to CW having the same energy over the same exposure times also elicited similar effects. Briefer exposures (0.4 or 0.8 seconds) to more intense peak power pulses did result in a rear limb paralysis pattern not seen in the longer exposures (4 to 8 seconds) of equal energy. These results suggest that these types of neurological deficits are not selective for high peak power pulses and can be largely explained in terms of bulk thermal effects, except for the case of the rear limb paralysis.

4. Evoked Reflexive Movements: Utilizing the WRAIR waveguide exposure system that can induce temporal peak SAR values of up to 20 megawatts/kg (at 1250 MHz) localized to the center of a mouse brain, we have explored the specific effectiveness of such pulses in evoking reflexive movements. BALB-C mice (weighing 15-20 g) were constrained within a modified 60 cc syringe cylinder and their body movements monitored by means of a tail clamp attached to a motion transducer. This system not only monitored "tail flicks" but all other body movements as well, even slight respiratory movements and the arterial pulse. Brief multiple pulse bursts of varying numbers of pulses were sequentially applied until a threshold for evoking reflexive movements was clearly identified. The exposures began with microwave pulse bursts that were subthresholds (too short) for eliciting reflexive responses. The number of pulses per burst was then sequentially raised (doubled each time) until a clear body movement was evoked. In order to confirm that a given pulse burst was consistently effective in evoking body movements, it was repeated 5 times at an interval of 10 seconds. Five repetitions of pulse bursts with a lower number of pulses were also delivered so as to "bracket" the threshold pulse count needed to evoke reflexive movements. Once such a threshold was clearly established, the individual pulse parameters were reset (e.g., from 200 KW into the waveguide at 1 usec pulse width to 20 KW at 10 usec). In this way it was possible to judge the relative effectiveness of microwave bursts with various pulse durations and amplitude combinations having the same energy content. A separate set of experiments was carried out using CW microwave exposures. Since the exposure system did not allow for rapid conversion between pulsed and CW modes, the CW exposures were performed one day after the pulsed exposures.

The experiments using high peak pulse to low average power ratios focused on three specific sets of pulse parameters as shown in Table 1.

TABLE I: PULSE PARAMETER (EVOKED)

Peak SAR	Pulse Duration	Pulse Rep.Rate
20 MW/kg	10 usec	80 pps
20 MW/kg	1 usec	80 pps
2 MW/kg	10 usec	80 pps

In most of the experiments, single 20 MW/kg, 10 usec pulses were applied at the outset of the experiment. The test mice usually responded to these single pulses initially, but not repeatedly, apparently quickly habituating to this level of stimulation. Truly reflexive movements (i.e., repeatedly evoked) were not observed until a burst of 4 to 8 pulses was delivered. Occasional responses to "half-threshold" burst (fewer pulses) were probably due in part to the coincidental occurrence of spontaneous movements. These results proved to be quite consistent over a reasonable experimental period (20 to 30 minutes). The same number of pulses were needed to reach the threshold for identical sets of pulse parameters at the beginning and end of an experiment.

Once a threshold pulse count had been ascertained for the 20 MW/kg 10 usec pulses, the same procedure was followed using 20 MW/kg, 1 usec pulse bursts, except that pulse count was started at 10 pulses per burst, then 20, 40, 80, etc. In terms of the total number of pulses per burst needed to repeatedly elicit reflexive body movements, 40 to 80 of these narrower pulses seemed to be the threshold range. After returning to the 20 MW/kg, 10 usec pulses for a repeatability check, the pulse parameters were reset to 2 MW/kg and 10 usec. The sequence of delivering 10, 20, 40, 80, 160 pulses was repeated. These wider, but less intense pulses, were not quite as effective as the other pulses since it often required 80 to 160 pulses to repeatedly elicit movements - about a twofold difference in total energy per burst.

We were concerned that differences in the responses to the three different pulse patterns might result from the sequence in which they were presented in any given experiment, e.g., the lower sensitivity to 2 MW/kg, 10 microsecond could have been due to desensitization produced by the previous exposures. In order to rule out this factor, several of the experiments, were carried out in "reverse order." Within the uncertainties of this experimental design, it did not appear that the sequence in which the three different pulse patterns were presented influenced the results.

Using mice drawn from the same population, but not previously exposed, the experimental protocol was repeated for CW exposures, using intensities that matched the average powers of the pulse bursts as shown below in Table 2.

TABLE 2: EQUIVALENT AVERAGE POWER

Pulses*	CW Equivalent
20 MW/kg, 10 usec	16.0 KW/kg
20 MW/kg, 1 usec	1.6 KW/kg
2 MW/kg, 10 usec	1.6 KW/kg

* 80 pulses per second

It was consistently found that CW exposures having equivalent energy content to the threshold pulse bursts were ineffective in evoking reflexive movements. For example, 16 KW/kg delivered for 0.1 second was equivalent in energy to the 8 pulse burst but did not result in repeatable movements. When the duration of the CW exposure was increased, by about 10 fold, movements were seen, but they were of a different nature. Rather than seeing 4 or 5 discrete responses to a sequence of 5 CW exposures spaced 10 seconds apart, a more diffuse movement pattern was seen. Under these conditions the mice continued to move around throughout the entire sequence and for a minute or so thereafter. These "agitation" type of movements may well have been due to seizure induction, however, the animals were not visible during exposure in the waveguide, so this implication is not assured.

Conclusions

The energy density associated with pulse burst found to be effective in eliciting reflexive movements was in the range of 0.8 to 1.6 joules/gm which for these short bursts would lead to temperature elevations of 0.2 to 0.4^{o}C.

TABLE 3: THRESHOLDS FOR REFLEXIVE MOVEMENT

Pulse Duration (usec)	Peak SAR (MW/kg)	Burst Number of Pulses	Energy Per Burst (Joules/gm)	Burst Duration (msec)
10	20	4-8	0.8-1.6	50-100
10	2	80-160	1.6-3.2	1000-2000
1	20	40-80	0.8-1.6	500-1000
CW	0.016	-	16	1000e

While these are not thermally inconsequential levels, they are far below the "thermally stressful" levels we have previously reported to be associated long lasting (many minutes) or irreversible neural deficits. Thus it appears that these reflexive movements are due to stimulation by pulsed microwaves, of neural elements rather similar to electrical stimuli conventionally used in neurophysiological studies.

This pulsed microwave neural stimulation phenomenon could not be replicated using equivalent CW energy inputs. This indicates that it is the high intensity (or energy) of the individual pulses, rather than the average intensity of the burst, which leads to the neural stimulation. The fact that the 20 MW/kg, 1 usec, pulses were somewhat more effective than the 2 MW/kg, 10 usec pulses, further suggests that it is the peak power rather than the pulse energy which is the salient factor in achieving neural stimulation.

These results might be attributable to "microwave hearing" phenomena since it has been shown that pulses of this sort can produce thermoelastic waves leading to ultrasonic energy bursts and possibly subharmonic "audible" clicks. However, it is difficult to explain why 4 to 8 such clicks would be effective in evoking movements while 1 or 2 such clicks are not. A more likely explanation for these results might be that temporal summation of subthreshold depolarizations, produced by individual pulses, are causing changes in neuronic firing patterns.

While these effects are far removed from the "damaging" levels associated with longer lasting neural deficits, they do pose a potential hazard to personnel exposed to them. This hazard would be in the form of a disturbance of neural information processing that would lead to a decline in "operational performance" ability. If such operations are of a critical nature they could jeopardize the well-being of the exposed person as well as others depending on his task performance abilities. Conversely, these microwave stimulation effects might prove to have a beneficial value in a medical context. Microwave stimulation of the motor cortex could conceivably prove to be of value in overcoming the paralytic effect of strokes or traumatic head injuries. Such medical applications are obviously quite speculative at this point, but may be worthy of future investigation.

Proposed Future Research

As part of the preceding (Phase 3) studies, we were able to demonstrate clear thresholds for reflexive body movements that are evoked by various patterns of microwave pulsing. Our results suggest that high peak power pulses are sightly more effective than less pulses with lower peak power, but longer duration pulses. Equivalent energy exposures to CW were totally ineffective. In addition to seeking further verification of these phenomena, we propose to refine the successful methodology we used in order to explore other physiological responses of interest, such as microwave evoked cardio-respiratory reflexes and microwave modification of evoked response to light and sound stimuli.

The conclusions we drew regarding the relative ineffectiveness of CW versus PW (Pulsed RF) were based on experiments on different sets of animals exposed on different days. Improvements in the exposure system (scheduled for March of 1988) will allow for rapid switching between the CW and PW exposure modes. Experiments in which responses to CW and PW can be compared sequentially in the same animal would appropriately test the validity of our present conclusions.

During the research project just completed, we developed an arterial pulse detector based on an inflatable cuff positioned around the base of the mouse tail. This technique worked reasonably well, but it produced a rather complex signal from which extraction of heart and respiratory rate was difficult. A standard "cardiotachometer" circuit could not be used reliably, and it seemed that a more sophisticated, computer based, analysis would be appropriate. In particular, we proposed to perform a Fourier transform on short segments (about 10 seconds) of arterial pulse records just before and just after microwave exposure. The two main frequencies in the signal spectrum should be the cardiac and respiratory rates. Shifts in these two peaks should represent reflexive (autonomic) responses to an exogenous event, which in this case would be the brief microwave exposure. Thresholds for cardiorespiratory responses to various microwave pulsing patterns could then be ascertained and compared to those seen for the motor responses.

It is possible, even likely, that microwave pulse trains of lesser energy than those required to evoke body movements could "modulate" responses to other nervous system inputs. In order to explore this possibility, we propose to pair microwave pulse trains (and equivalent CW) with light flashes and or sharp sounds which normally produce "startle reactions." These startle reactions will be monitored using the body motion and cardiorespiratory reflex detection systems previously employed.

Thresholds for microwave sensitivity can then be ascertained by noting the highest microwave energy levels at which no difference in the two response patterns is seen. These experiments would serve to delineate the extent to which microwave exposure might degrade "operator performance" - i.e., the ability of personnel to respond appropriately to visual or auditory signals.

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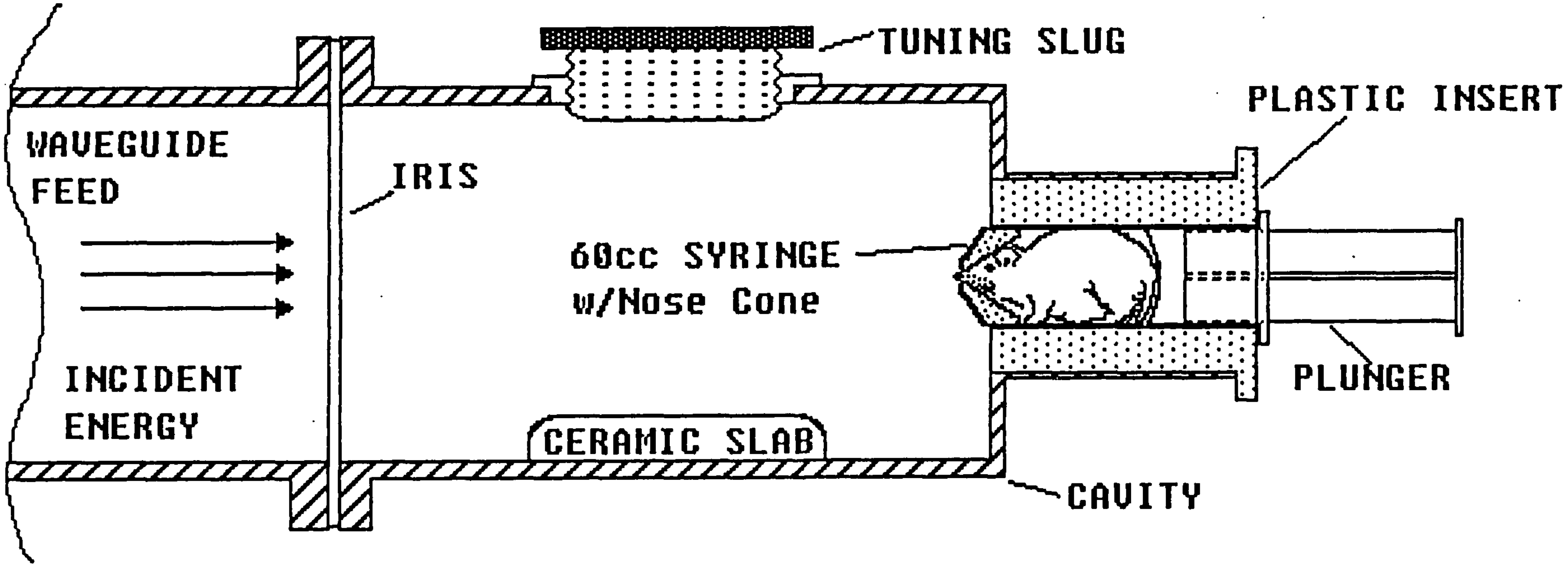

FIGURE 1: Resonant Cavity (WR650) waveguide feed at 1.25 GHz