PHYSICAL MECHANISMS OF THE ACTION OF INTENSE ULTRASOUND ON TISSUE[1]

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It is now well known that intense ultrasound, when properly controlled, can produce unique results in biological systems. An example of this is the high intensity ultrasonic method of producing selective, accurately localized alterations in brain tissue by focusing the acoustic energy in the region to be affected (1, 2, 3). Figure 1 is a tissue section of the brain of a cat which shows a lesion approximately 1.0 mm. in diameter interrupting the mammillothalamic tract. To produce this lesion, converging ultrasonic beams entered the brain from the top and traversed three quarters of the brain thickness before coming to a focus at the site of the lesion. No alteration occurred to intervening tissue. This method now constitutes a unique tool for neurological research and human neurosurgery.

If the full potentialities of such new methods, for fundamental research and for medicine, are to be realized, it is essential that the physical mechanism of the action of intense ultrasound on tissue be understood. In order to elucidate the physical mechanism, a comprehensive investigation involving the determination of the ultrasonic dosage relations required to produce a given functional endpoint in a young mammal has been undertaken at the Biophysical Research Laboratory of the University of Illinois. Dosage relations can be expressed as the time duration of exposure as a function of the acoustic variable, i.e., intensity, pressure, particle velocity, etc., under specified environmental conditions for production of the specific endpoint.

Since mammals are probably the most important animal class to which the new ultrasonic methods will be applied, it is desirable that a representative of this group be used in these investigations. The young mouse, 24 hours after birth, is a convenient preparation for a number of reasons, one of the more important being that it is an essentially poikilothermic animal and as such can be carried through temperature cycles to as low as 0°C. without producing permanent changes. The mice are irradiated at the third lumbar vertebra. This level of the cord is the approximate center of the lumbar enlargement which contains a high density of the motor neurons associated with the femoral, sciatic and obturator nerves. Thus, alteration of the motor neurons of the lumbar enlargement produces motor paralysis of the hind limbs of the animal. Paralysis of the hind limbs then serves as an easily detected and unambiguous functional endpoint for an ultrasonically induced effect in the irradiated animals. Figure 2 shows an animal supported in the mouse-holder in preparation for irradiation.

In these experiments, the variation of the acoustic intensity in the plane traveling wave field over the entire lumbar enlargement is less than 5 per cent. The base temperature of the animal is held to ±0.1°C. These experiments are performed in the absence of cavitation. Results have been obtained at a frequency of 982 kc/s, a hydrostatic pressure of one atmosphere and base temperatures of 2°C., 10°C. and 20°C. The data show that a rather well-defined threshold region exists for each base temperature. The threshold region can be defined as follows: If a large number of animals are irradiated with identical values of the acoustic field variables for various periods of time, and the percentage of animals paralyzed at each duration of exposure is plotted as a function of the reciprocal of the time duration of exposure, a sigmoid curve is obtained. Figure 3 is a typical curve obtained in this fashion. Each plotted point represents approximately 25 animals. The curve through the points is obtained by standard statistical treatment of the data.

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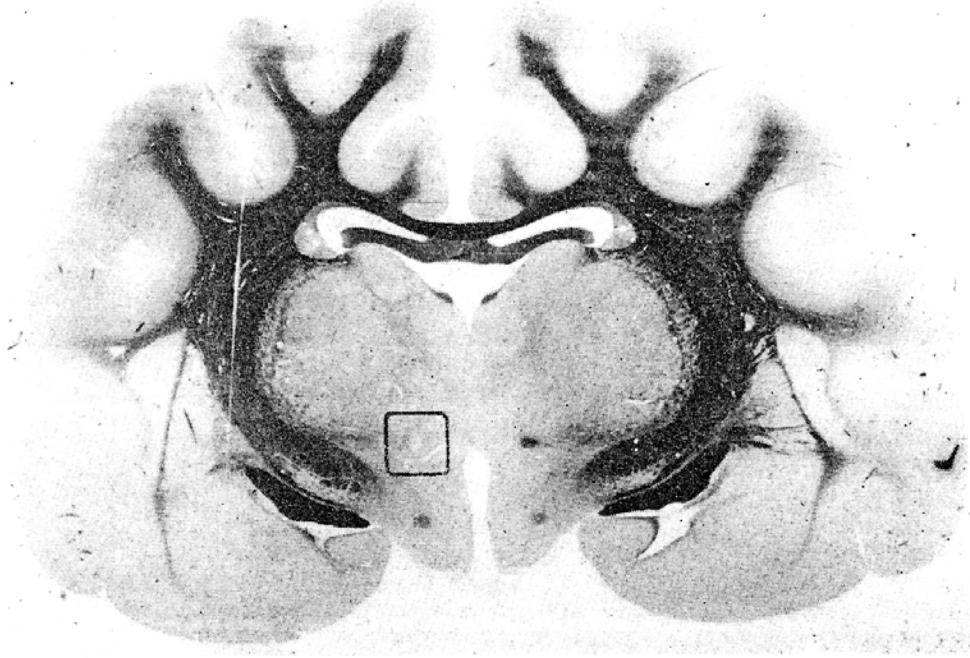

FIG. 1. Interruption of the mammillothalamic tract in the brain of a cat by properly controlled, high intensity, focused ultrasound. Compare the lesion produced by ultrasound on the left side with the untreated right side.

From curves such as this one, a threshold range can be arbitrarily defined as the range of exposure times from 10 per cent of the animals paralyzed to 90 per cent of the animals paralyzed. The collection of these threshold ranges, obtained for various values of a specific acoustic variable, then defines the threshold region. Figure 4 shows the threshold region for the base temperature of 10°C. The ordinate is the reciprocal of the exposure time and the abscissa is the square root of the acoustic intensity. The plotted points (indicated by a +) are obtained from sigmoid curves similar to the one just shown, but obtained at other values for the acoustic intensity. The threshold region is seen to display a "linear portion". For the curve of 50 per cent of the animals paralyzed, the "linear portion" extends from approximately 48 watts/cm^2 (25 seconds time duration of exposure) to at least 160 watts/cm^2 (0.8 second time duration). A statistical analysis indicates that this is a linear relationship to a high degree of accuracy. The width of the threshold region in the linear portion is only 17 per cent. This includes the uncertainties in the physical measurements as well as the biological variation of the animals.

In the course of these studies, measurements were made of the temperature rises in the spinal cords of the mice as a function of ultrasonic dosage (4). This was accomplished by imbedding small thermocouples in the cords. The greatest temperature rises observed are shown in figure 4, plotted at the corresponding dosage coordinates (circles). Figure 5 shows the 50 per cent paralysis curves for base temperatures of the animals of 2°C., 10°C. and 20°C. The maximum observed temperature rises are also shown. The width of the threshold region, for each of the three base temperatures, is less than 18 per cent.

Histological studies have also been carried out on these irradiated animals. These studies show: a) that there is an excellent correspondence between the appearance of a lesion in the lumbar enlargement of the cord and the observed functional change, i.e., all animals which show a loss of motor function of the hind legs also display a lesion in the lumbar enlargement, and b) that in sacrificing animals for various periods of time after irradiation, it is found that the histological lesions appear after approximately 10–15 minutes following irradiation, whereas the functional change is observed instantaneously.

Concerning the present status of our understanding of the physical mechanism of the action of intense ultrasound on tissue, the following statements can be made:

I. Cavitation may be eliminated since these data were obtained in the absence of any phenomena suggesting the presence of cavitation. Also, earlier work (5, 6) performed at this

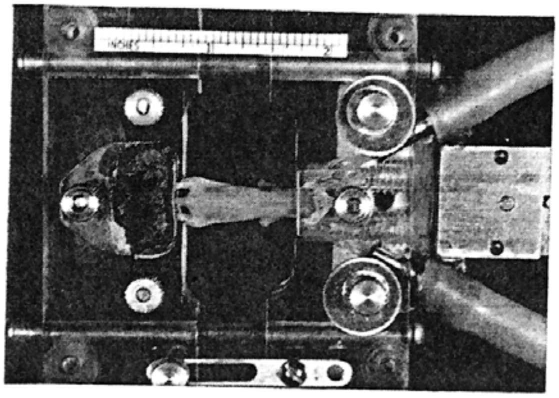

FIG. 2. An infant mouse supported in the mouse-holder ready for irradiation.

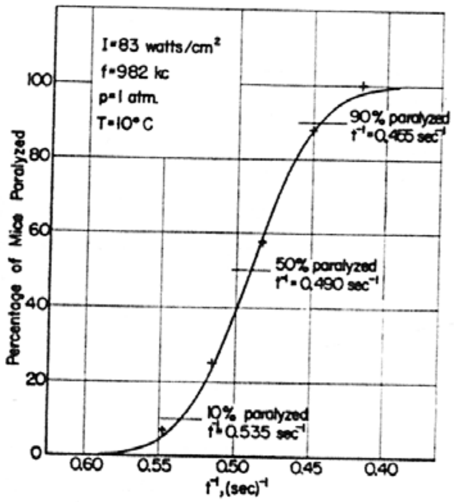

FIG. 3. A typical sigmoidal distribution curve of the percentage of mice paralyzed as a function of the reciprocal of the time duration of exposure.

laboratory, in which animals were irradiated under a hydrostatic pressure sufficiently high to prevent tension forces from occurring in the tissue, demonstrated that this phenomenon does not contribute to the physical mechanism.

II. In the linear portion of the threshold region, the maximum temperatures developed in the cord are considerably less than the normal temperature of the adult animal, viz., approximately 36°C. Hence, a thermal process may be considered unimportant as the primary mechanism in this region.

III. The linear portion of the threshold region displays a relationship showing that the reciprocal of the exposure time is proportional to one of the acoustic field variables, pressure amplitude, particle velocity amplitude, particle acceleration amplitude, etc. However, at the present time there is insufficient information to enable one to make a decision regarding the relative importance of these acoustic variables.

IV. The form of the dosage curve in the nonlinear portion suggests that a process different from that obtaining in the linear region may be involved.

V. Since the lesions appear histologically

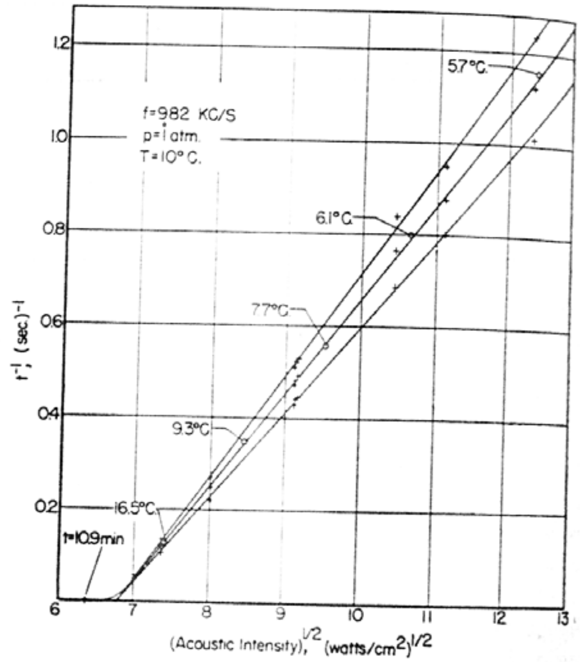

FIG. 4. The threshold region of paralysis of the hind legs of mice under ultrasonic irradiation at the base temperature of 10°C. The indicated temperature rises were measured by thermocouples imbedded in the spinal cords of irradiated mice.

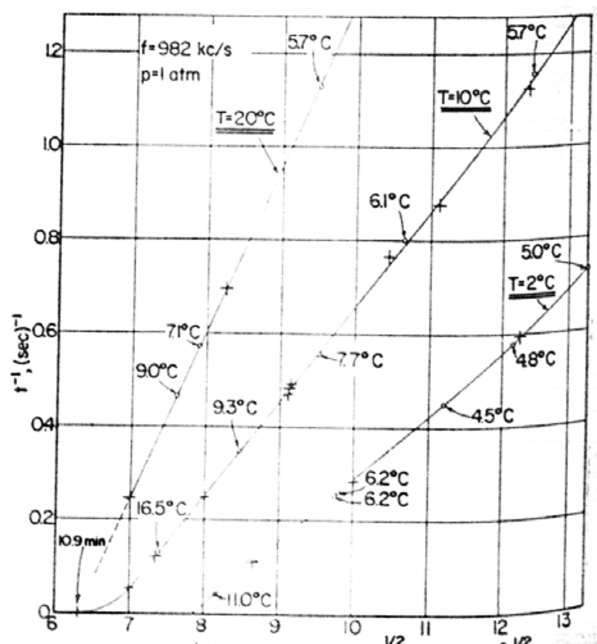

FIG. 5. The 50 per cent paralysis curves for base temperatures of the mice of 2°C., 10°C. and 20°C. The maximum observed temperature rises are also shown.

approximately 10–15 minutes after the loss of function has occurred, it would appear that the site of the physical action is a submicroscopic structure and that the ensuing histologically observed change is associated with secondary processes.

VI. A simple theory (7), which assumes that the observed effects are produced by unidirectional forces of the sound wave, which cause elastic failure in the system when a structural component is displaced from an initial equilibrium position to a second position from which recovery cannot occur, is not supported by the experimental results presented in this paper (8).

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