Use of focused ultrasound for stimulation of nerve structures

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Pulsed focused ultrasound can stimulate the receptor and conductive nerve structures of humans and animals as well as the neurons of the central nervous system of invertebrates. The possibility of a wide practical use of this method in medicine and physiology is considered. For example, the stimulating ability of focused ultrasound is applied to the diagnosis of neurological diseases, to the study of skin and tissue sensitivity in man, to the diagnosis of hearing disorders, and to the introduction of auditory information to the deaf with certain forms of hearing pathology. The factors that affect focused ultrasound as a stimulus for the irritation of nerve structures are discussed.

KEYWORDS: ultrasonics, nervous system, deafness

Introduction

The great potentials of using focused ultrasound in medicine and biology for the local destruction of predetermined deep structures in humans and animals are well known[1-3]. However, over the last ten years an independent and probably even more promising field of the medical use of focused ultrasound has formed. In the early 1970s a new trend in biomedical acoustics emerged in the USSR relating to the use of focused ultrasound for non-contact, non-electrode stimulation of various human nerve structures in order to diagnose and treat diseases. The literature available on this subject, numbering dozens of titles will, with a few exceptions, be almost unknown to a foreign reader. This work reviews the most substantial results obtained to date in this comparatively new and promising field.

Focused ultrasound as artificial stimulus

Electrical current as an artificial stimulus of nerve structures has found wide use in laboratory and clinical practice and has promoted considerable progress in medicine and physiology. However, a significant disadvantage of this method is that the stimulation of deep nerve structures requires a preliminary operation to introduce the electrodes. Therefore, the search for stimulation methods that do not require direct contact between the stimulation device and the structure is of great scientific and practical interest.

In the early 1970s it was shown[4-9] that pulses of focused ultrasound, with a duration of the order of milliseconds could stimulate various peripheral receptor structures in man. Beginning in 1975[10], and in a number of further works[11-18], it was shown that focused ultrasound could stimulate the receptor structures of the labyrinth in the internal ear in man and animals, as well as the fibres of the auricular nerve. This formed the basis for developing new methods for the diagnosis of aural diseases and hearing prosthesis.

The main advantages of the ultrasonic method for the stimulation of nerve structures are: there is no need for an operation to get to deep structures, and there is a precise control of stimulus characteristics—intensity, time, and stimulation area. All this holds a great deal of promise for the application of focused ultrasound as a stimulus of nerve structures.

Equipment and methods

Figure 1 illustrates the ultrasonic generator developed by our laboratory for medical purposes and intended for focusing transducers. Although comparatively small in overall size (250 × 304 × 110 mm) and weight (8 kg),

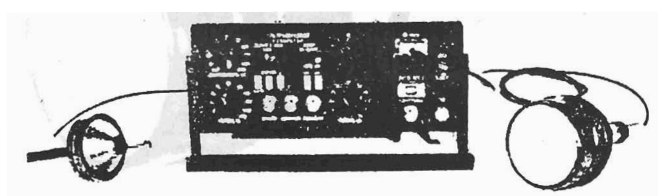

Fig. 1 Ultrasonic generator for focusing systems

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this generator provides at least 100–150 W acoustic power to the transducer. The ultrasonic operation frequency is from 0.5 to 3 MHz. The diameter of the focal spot is 6 mm for 0.5 MHz and 1 mm for 3 MHz. This implies that with the above-mentioned acoustic power the ultrasonic intensity, averaged over the focal spot area, can reach 400 W cm^{-2} at a frequency of 0.5 MHz, and 7500 W cm^{-2} at a frequency of 3 MHz. (The peak value of the ultrasonic intensity in the centre of the focal region is about four times greater than the above-mentioned averaged values.)

The generator provides continuous and pulsed operations with various durations of pulses and repetition frequencies. It also supplies both a single pulse operation with a predetermined pulse duration (from 0.01 to 5000 ms), and amplitude-modulated oscillations with audio modulation frequency. The voltage on the focusing transducer changes in steps every 1 dB up to 55 dB. It is also possible to connect up external square pulse generators and audio-signal generators; this substantially broadens the possibilities of the equipment.

The characteristic feature of the instrument is that it affords a rapid change of one focusing transducer, with a resonance frequency in the range of 0.5–3 MHz, for another one. At the same time the resonance frequency is automatically established with the matching of the generator output cascade to the radiator. This provides a means for a quick investigation of the frequency dependence of the observed physiological or biological effect, offering useful information for understanding the mechanism of the phenomenon.

Figure 2 shows some modifications of the focusing transducers designed by our laboratory. Fig. 3 illustrates such a transducer, the frame of which incorporates a mechanism that makes it possible to

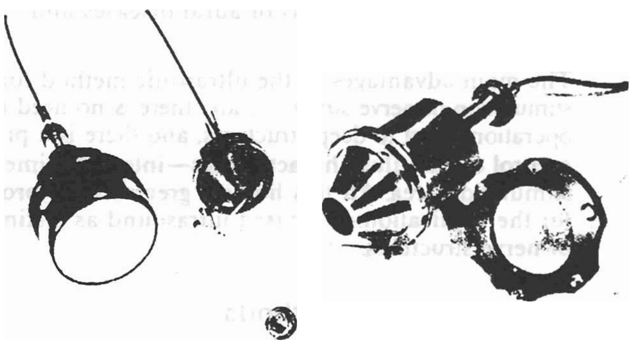

Fig. 2 Ultrasonic focusing radiators for use in medicine and physiology. The size of the coin is 2.5 cm

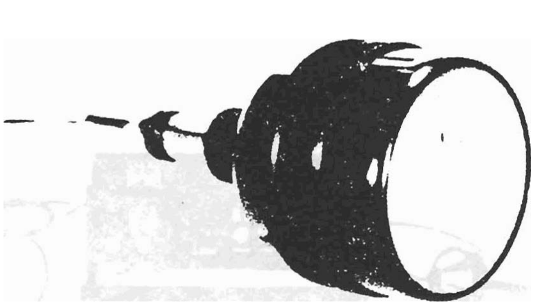

Fig. 3 Radiator that enables the immersion depth of the focal region in biological tissues to be changed

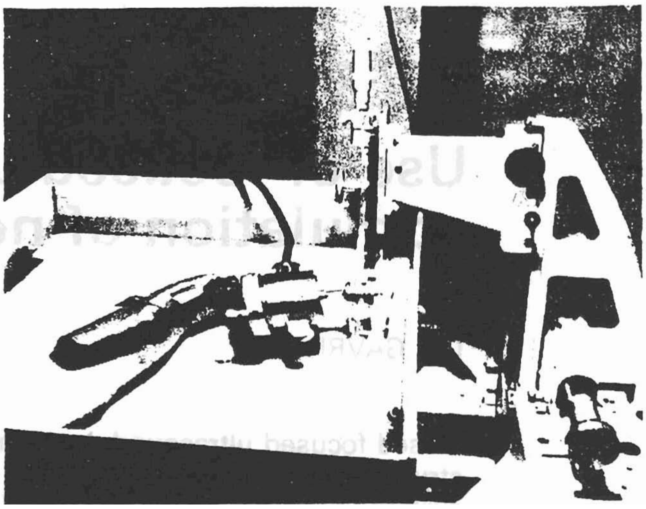

Fig. 4 Part of the experimental unit for studies of skin sensitivity in man

Fig. 5 Experiment on stimulation of nerve structures of the auditory system

change the depth of the focal region, in the tissues of the organism, within the range of 0 to 50 mm.

The procedural peculiarities of using focused ultrasound for the stimulation of nerve structures are described at length in Refs 6 and 16. For instance, when skin and tissue sensitivity was studied, the forearm of the subject was fixed in a specially made mould and placed in a water-filled bath (Fig. 4). The temperature of the water was controlled thermostatically. For a precise placing of the focal region into coincidence with a predetermined sensitive point, a special coordination device was used. The points were marked on the skin by a special marker and then transferred onto life-size 'cards'—photographs of the hand[8]. The 'cards' made it possible to act repeatedly with ultrasound on one particular point.

In order to stimulate the nerve structures of the auditory system, amplitude-modulated focused ultrasound was applied[16]. The subject assumed a horizontal position (Fig. 5) and the transducer, which was placed in a bag with heated water, made contact with the head of the subject. Possible ultrasonic defocusing and attenuation in the overlying bone have been left out of this account. In order to align precisely the acoustic axis with direction at the internal ear, a special coordination device was also used.

However, such labour-consuming methods and comparatively complex experimental units were necessary only for running preliminary laboratory investigations that required particularly high reproducibility and reliability of results. Under clinical conditions, the examination can be carried out in a much simpler way, and by using the developed ultrasonic equipment it can be effected near to the patient's bed.

Stimulation of skin and tissue receptors

Using pulses of focused ultrasound directed towards the sensitive points of a person's arm, sensations will be produced, the character of which depends on the parameters of the ultrasonic action and the localization of the focal region[4-9]. By applying different ultrasonic intensities for different times it is possible to evoke all the sensations that man can perceive through his skin: tactile, tickling, temperature (warmth and cold), pain, etc. Pain can be evoked by the focused ultrasound stimulation of not only the surface nerve structures, but also the deep ones.

Investigations by means of focused ultrasound yielded data that are of interest for reception physiology. For example, psycho-physical studies showed[6-8,19] the presence of 'universal' temperature-sensitive points that can be related to hot and cold sensations, as distinguished from the widespread conception that there are separate hot and cold points. It turned out that the modality of temperature sensations (warmth, cold) depends on ambient temperature, and temperature-sensitive points can function as warm or cold ones depending on the environment.

In determining tactile thresholds on the arms of healthy people it was found that the thresholds increased in the direction from fingers to forearm[20,21]. An extremely important result in the physiology of tactile reception was that in none of the sensitive points on the forearm was the threshold the same (or close) to the value on the fingers and palm. This result in combination with the published data on the structure of skin receptors suggests that the threshold value depends on the density of the receptors distributed on the skin surface rather than on their morphological features[20,21].

By directing the focal spot of the radiator into different tissues it was found that a normal man had individual forms of pain differing from each other in thresholds, character of irradiation and sensation[8,16]. These data open up possibilities for clinical investigations of the changes in pain thresholds with various diseases of internal organs.

Diagnosis of neurological diseases

The ultrasonic method was employed to diagnose a number of neurological diseases relating to changes of skin sensitivity[22]. The frequency of ultrasound was 1.95 MHz. A comparison was made between tactile sensations on the skin of the fingers in a control group of 21 healthy people, and 30 patients with eight forms of neurological diseases. All the patients showed deviations from normal of tactile sensitivity, ranging from a considerable increase of tactile thresholds up to the entire absence of tactile sensitivity.

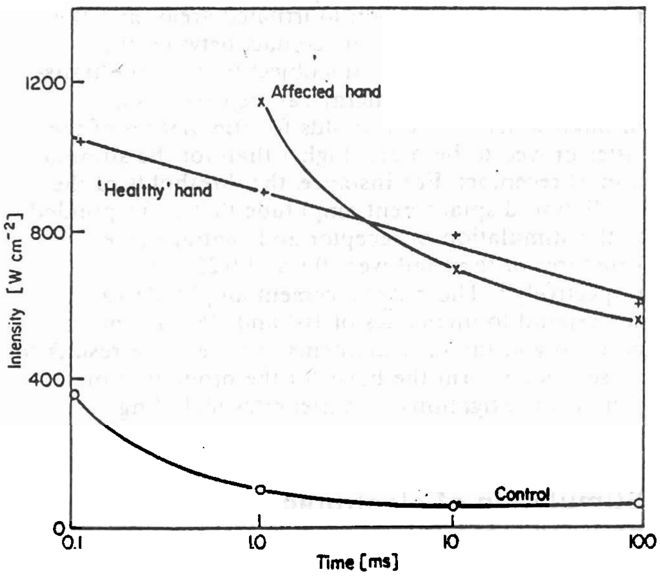

Fig. 6 Tactile sensitivity thresholds in the patient with syringomyelia. O — thresholds in normal people (control group); X — thresholds in the right (affected) hand; + — thresholds in the left hand, where clinico-neurological examination showed no sensitivity disorders

As an example, Fig. 6[22] presents the results of an examination of the tactile sensitivity in one of the patients with syringomyelia. The y-axis is the intensity of ultrasound in the focal region, and the x-axis is the stimulus duration. It can be seen that with a stimulus duration of 0.1 ms the tactile sensitivity on the right (affected) hand was absent even at maximum intensities (1400 W cm^{-2}). It can also be seen that on the left hand, where standard clinical examination showed no sensitivity disorders, there was a considerable deviation from normal.

As a result of these investigations it was possible not only to characterize quantitatively the extent of sensitivity disorders for every form of pathology, but also identify 'subclinical' disorders that traditional methods failed to record.

Attempts at stimulation of central nerve structures

The possibility of using focused ultrasound for the stimulation of central nerve structures has long attracted the attention of researchers[23,24]. In a number of works various functional effects occurring under the action of focused ultrasound on the brains of animals were obtained and investigated[25-28]. However, until recently attempts at obtaining direct proof that ultrasound could stimulate central nerve structures have been unsuccessful.

Only recently have experiments on invertebrates (edible snails without shells) showed the possibility of using focused ultrasound for the stimulation, not only of receptor structures, but also of central nerve structures[29,30]. The snail has the following merits: accessibility for microscopic observation of irritated areas, ease of electrode introduction, simplicity of matching the focal region to irritated areas, and the possibility of good acoustic contact between the focusing transducer and the object because the transmission of ultrasonic energy can be carried out through water. The thresholds for stimulation of the latter proved to be much higher than for the stimulation of receptors. For instance, the thresholds of the oscillation displacement amplitude that corresponded to the stimulation of receptor and central nerve structures of the snail were 0.1 and 0.25 μm, respectively[29]. These displacement amplitude values correspond to intensities of 160 and 1000 W cm^{-2} according to the measurements in water. The results of these studies form the basis for the promotion of similar investigations on vertebrates including mammals.

Stimulation of electroreceptors and photoreceptors

A study was made of the effects occurring under the action of focused ultrasound on the structures of the electroreceptor system in skates[31]. Pulsed ultrasound, acting on the region of the electroreceptor pore, induced spike activity, but in continuous operation this activity was absent. When the electroreceptor acted on the ampulla, there was a change in the spontaneous activity only in the continuous operation. This was found to be due to the thermal effect of ultrasound.

As far as the stimulating effect of focused ultrasound on the retinal photoreceptors is concerned, the results obtained were found to be conflicting. Recent experiments carried out using our equipment[32] failed to produce this effect. These data do not support the results previously published by Bertenyi et al[33].

Introduction of auditory information to the deaf

It is known that 3-5% of the population in developed countries suffer from deafness and hearing disorders. In combating this affliction much success has been achieved. New methods of operative and medical treatment are appearing, and more and more improved models of hearing aids are being designed. However, there is a large group of practically deaf people for whom the existing means are either ineffective or of little effectiveness. It has been with just this aim, assisting such people, that an attempt has been undertaken to use ultrasonic methods for hearing prosthesis.

In the initial experiments on frogs it was shown[10] that under the action of focused ultrasound stimuli on the internal ear the auricular centres of the brain responded with electrical reactions similar to the responses from auditory stimuli. The ultrasound intensities applied in these experiments were a factor of 10^2–10^3 lower than the intensities that cause structural changes in the labyrinth and brain[34]. Therefore, the conditions of the ultrasound action do not present a direct danger to the organism.

In the course of further investigations a new method for the introduction of auditory information to man has been suggested[11,13]. The essence of the method lies in the fact that amplitude-modulated ultrasonic oscillations are directed to the labyrinth: the carrier frequency in this case is far above the upper limit of the frequencies perceived by man (for instance, from 0.5 to 3 MHz) and the modulation frequency corresponds to the transmitted auditory information. In essence this method has no limitations in the frequency of modulating (audio) signals. Under the action of focused ultrasound, modulated in amplitude by oscillations of a complex form (for example, signals from a microphone, tape recorder, etc) on the internal ear, normal people hear the transmitted undistorted acoustic information (speech, music).

The threshold intensities of amplitude-modulated ultrasound corresponding to the emergence of aural sensations in man at different frequencies of modulating voltage and modulation factors, as well as at various frequencies of the ultrasonic carrier, have been determined[16]. For instance, at an ultrasonic frequency of the order of 0.5 MHz the threshold intensities in the focal region account for 0.01–0.1 W cm^{-2}, ignoring attenuation of ultrasound in biological tissues.

The most substantial result is that by means of focused ultrasound it is possible to stimulate through the skull not only the receptors (hair cells) of the internal ear, as with ordinary sound stimulation, but also auditory nerve fibres, which until recently could be stimulated only by implanted electrodes. This significant result was supported by experiments on animals with previously destroyed receptor systems of the labyrinth. In the midbrain auditory centres in animals the responses to the ultrasonic stimulation were recorded, and were found to be comparable with responses from the normally functioning receptor system, but with higher thresholds[17,18]. Histochemical methods confirmed that in the case of receptor system disorders ultrasound did activate the nerve fibres[18].

Finally, the possibility of direct stimulation of auditory nerve fibres by ultrasound is supported by the fact that the deaf whose receptor system is diagnosed to have been destroyed, may perceive auditory information delivered by means of amplitude-modulated ultrasound, whereas standard hearing aids cannot help them[16].

When using ultrasound for an active influence on human beings, it is very important to define the potential hazards of ultrasonic radiation. Our investigations concerning morphological[34], physiological and histochemical[18] changes under ultrasonic action show that presently there are no insuperable obstacles in the path of the practical use of focused ultrasound for nerve structure stimulation.

Diagnosis of aural diseases

The possibility of using ultrasound not only for the stimulation of receptors, but also for nerve fibres of the auditory system is very important for clinical diagnosis in order to determine hearing disorders at different levels.

A comparison was made between frequency – threshold curves obtained by means of amplitude-modulated ultrasound and the curves of audibility thresholds obtained by sound stimulation of the labyrinth[16]. For subjects that hear normally these curves are comparable, despite some differences. It should be noted however, that for subjects with various forms of hearing disorders the curves differ greatly.

For instance, Fig. 7[16] illustrates the audiogram and ultrasonic frequency – threshold curve of a patient

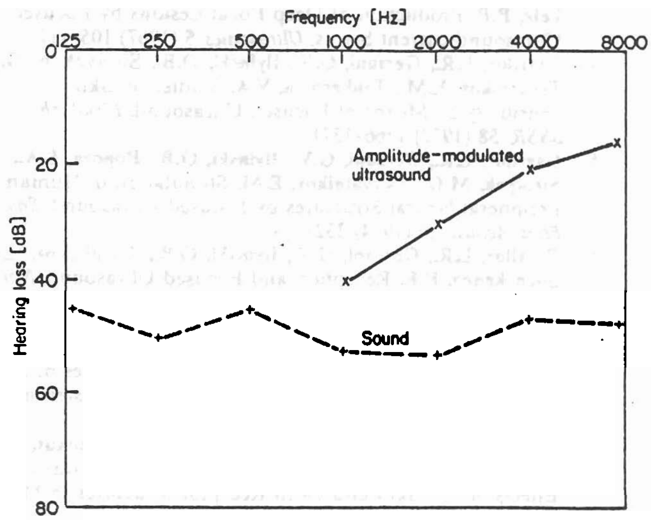

Fig. 7 Audiogram and ultrasonic frequency - threshold curve for the patient with otosclerosis. + — audiogram; X — ultrasound frequency - threshold curve

with otosclerosis. The y-axis presents the loss of hearing relative to the level of normal hearing, and the x-axis presents the frequency of tone or amplitude modulation of ultrasound. Otosclerosis is characterized by the absence of an auditory sensation at one or several ultrasonic modulation frequencies (for example, Fig. 7 - 125, 250 and 500 Hz) while the sounds of the same frequencies can be distinctly heard by subjects without otosclerosis. In the cases of other diseases the form of the ultrasonic frequency - threshold curves is rather individual. This fact is already being employed in clinical practice to diagnose not only otosclerosis, but also neurosensory hearing disorders, auditory neurinoma, etc.

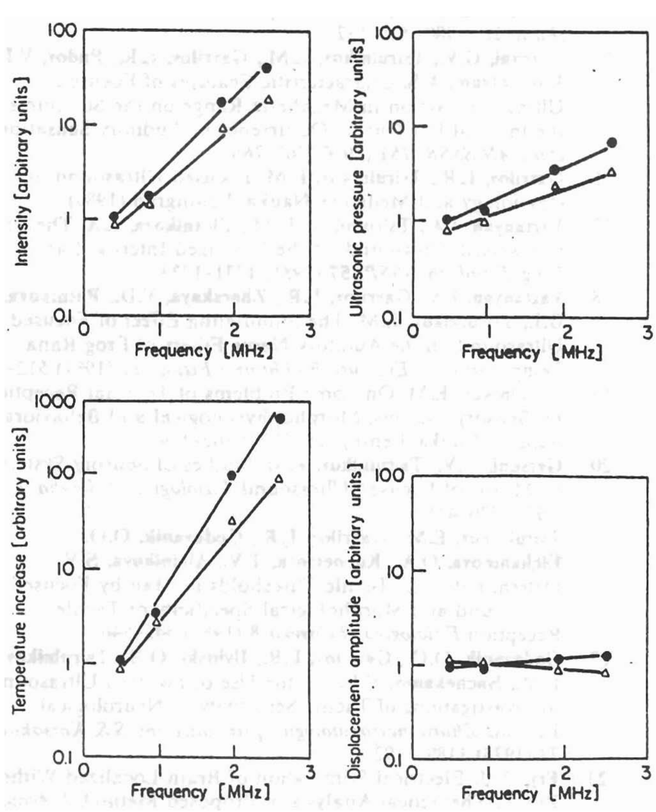

Fig. 8 Relative changes in the characteristics of focused ultrasound, which correspond to the emergence of tactile and thermal sensations in the hand at ultrasonic frequency of 0.5–2.5 mHz. Δ — tactile sensations; ● — thermal sensations

Possible mechanisms of focused ultrasound stimulation

A study was made of the factors of focused ultrasound responsible for the stimulation of skin receptors and the emergence of tactile, temperature, pain and other sensations.

Fig. 8[16] shows the relative changes in some characteristics of focused ultrasound at a frequency changing from 0.5 up to 2.5 MHz for tactile and thermal sensations on the human hand. The characteristics for a frequency of 0.5 MHz are assumed to be a unit. From the graph it will be obvious that only one characteristic — displacement amplitude — remains unchanged for every form of the sensations with frequency changing over a wide range. The rest of the characteristics (intensity, ultrasonic pressure, increment of tissue temperature, particle velocity, acceleration, radiation pressure, etc) change greatly, sometimes over a range of several orders of magnitude.

Below are some experimental data concerning the values of the amplitude of oscillation displacement in water that produce a threshold stimulation of peripheral nerve structures by means of focused ultrasound[6,16]:

Receptors of labyrinth (frog)	0.004–0.01 μm
Pacinian corpuscles (cat)	0.03–0.05 μm
Tactile sensations on the skin of human fingers	0.08–0.11 μm
Tactile sensations on the skin of a human palm	0.13–0.18 μm
Tactile sensations of the skin of a human forearm	0.2–0.58 μm
Warmth and cold sensations on the skin of a palm (depending on the ambient temperature)	0.43–0.6 μm
Pain: sensation on the skin of a palm	0.38–0.64 μm

However, the actual mechanism of the stimulation of the nerve structures under the action of ultrasound is most probably related to a certain unidirectional, 'rectified' action rather than a sign-alternating oscillation displacement of the medium *per se*. Indeed, the subjects could not differentiate between tactile sensations in response to a long stimulus or two short stimuli (for instance, a stimulus lasting 400 ms and two stimuli of 10 ms with an interval between them of 380 ms)[6,8]. The stimulus with the duration 400 ms evoked sensations only during switching on and off. A change of the carrier frequency at the same displacement amplitude exerted no effect on the character of sensations. However, the mechanism that transforms a sign-alternating displacement into a unidirectionally acting factor is still unknown. This mechanism is possibly related to purely physical processes. It is not excluded, however, that this transformation is of a 'physiological' nature rather than a physical one and is related to such well known physiological properties of nerve structures as refractory, adaptation, and masking.

Under the action of amplitude-modulated ultrasound on the internal ear other acting factors are added. First of all, it should be borne in mind that the hearing organ is an extremely sensitive instrument reacting to the action of adequate information (sound). Therefore, it is necessary to take into account the possible effect on it of the sound component, resulting from the radiation pressure of amplitude-modulated ultrasound. It is well known[35] that with the propagation of amplitude-modulated ultrasonic oscillations the radiation pressure appears to be the sum of three components: one constant and two variables. One of the variable components changes with modulation frequency and the other with double modulation frequency[35].

Thus, if the receptor system of the labyrinth in man functions normally, one of the most probable factors causing the occurrence of auditory sensations is the effect of sound frequency oscillations, arising due to the variable component of radiation pressure on the receptors. In this case, adequate (that is, sonic information), is channelled into the labyrinth, whereas ultrasound serves as a means of its delivery.

As has been mentioned above, amplitude-modulated ultrasound exerts a direct stimulating effect on the fibres of the auditory nerve[17,18]. The basic acting factor of focused ultrasound in this event still remains to be discovered. This may be the mechanical action of ultrasound that has been discussed above. However, a certain role of the transformation of ultrasonic oscillations into the electrical stimulus in this process cannot be ruled out. The physical character of this effect may be related to well known piezoelectric, or to be more precise, electromechanical properties of bone tissues[36,37].

Conclusion

The investigations carried out showed that focused ultrasound is a useful and promising means enabling the stimulation of both surface and deep nerve structures to be made. It is not improbable that in the near future there will be the emergence of a new broad field of ultrasonic medical diagnosis, based on precise measurements of thresholds for various sensations in a normal person, and a comparison with data obtained in another pathological case. Great social importance is attached to the possibility of using ultrasonic methods for hearing prosthesis, and the diagnosis of aural diseases in patients with disorders of the receptor system.

This method holds much promise for physiological studies. It is interesting to consider the possibilities for stimulation of visual, olfactory, taste receptors, nerve fibres and central nerve structures, as well as to investigate the mechanisms of thermal reception, thermal production and thermal regulation in humans and animals. Certain practical advantages may be gained from using focused ultrasound on acupunctural points for controlling the efficiency of anaesthetics by measuring the threshold of pain sensations before and after drug administration. At present it is reasonably difficult to circumscribe medical and physiological problems in which the stimulating effect of focused ultrasound may prove to be beneficial.

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