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Focused Ultrasound as a Tool to Input Sensory Information to Humans (Review)

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Abstract—This review is devoted to the analysis of studies and implementations related to the use of focused ultrasound for functional effects on neuroreceptor structures. Special attention was paid to the stimulation of neuroreceptor structures in order to input sensory information to humans. This branch of medical and physiological acoustics appeared in Russia in the early 1970s and was being efficiently developed up to the late 1980s. Then, due to lack of financial support, only individual researchers remained at this field and, as a result, we have no full- fledged theoretical research and practical implementations in this area yet. Many promising possibilities of using functional effects of focused ultrasound in medicine and physiology have remained unimplemented for a long time. However, new interesting ideas and approaches have appeared in recent years. Very recently, very questionable projects have been reported related to the use of ultrasound for targeted functional effects on the human brain performed in some laboratories. In this review, the stages of the development of scientific research devoted to the functional effects of focused ultrasound are described. By activating the neuroreceptor structures of the skin by means pulses of focused ultrasound, one can cause all the sensations perceived by human beings through the skin in everyday life, such as tactile sensations, thermal (heat and cold), tickling, itching, and various types of pain. Stimulation of the ear labyrinth of humans with normal hearing using amplitude-modulated ultrasound causes auditory sensations corresponding to an audio modulating signal (pure tones, music, speech, etc.). Activation of neuroreceptor structures by means of focused ultrasound is used for the diagnosis of various neurological and skin diseases, as well as hearing disorders. It has been shown that the activation is related to the mechanical action of ultrasound, for example, by the radiation force, as well as to the direct action of ultrasonic vibrations on nerve fibers. The action of the radiation force is promising for the realization of the possibility of blind and even deaf-and-blind people to perceive text information on a display using tactile sensations caused by ultrasound. Very different methods of using ultrasound for local stimulation of neuroreceptor structures are discussed in this review. Among them are practical methods that have been already tested in a clinic, as well as pretending to be sensational methods that are hardly feasible in the foreseeable future.

Keywords: focused ultrasound, sensory information, neuroreceptor structures, sensations, stimulation, radiation force, medicine, physiology.

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INTRODUCTION

Searching for artificial stimuli that can induce sensations noninvasively and locally has always been an important task of physiology and medicine. Such stimuli would be extremely useful in medicine, for example, in diagnosis of diseases associated with changes in various sensations, as well as in physiological studies. It is necessary to exclude any damage to the site affected by the stimulus or surrounding tissues, as well as to provide prolonged and repeated use of such artificial stimuli. It is important to perform accurate measurements of various parameters of stimuli.

Electric current has always played an important role as an artificial stimulus of neural structures. However, it is often impossible to use electric current for local stimulation of individual receptor or neural structures without affecting the neighboring area. In the case in which it is necessary to affect deep structures, surgery is needed to bring electrodes to them, which contradicts to the important biological requirement of noninvasive functional impact.

As shown below, the method of activating neuroreceptor structures with focused ultrasound entirely satisfies the requirements of contactless, noninvasive, local, and dosed effects. Functional effects arising from the use of ultrasound are extremely diverse. They

range from temporary reversible supression of functions to the appearance of a propagating excitation. The review is focused on the stimulating (i.e., activating or irritating) effect of focused ultrasound on the neuroreceptor structures that can be repeated many times (sometimes, for years) without any risk of damaging the structures and surrounding tissues.

REVERSIBLE EFFECTS AT THE ACTION OF ULTRASOUND

Functional (reversible) effects of the action of ultrasound on neuroreceptor structures have been well known since the middle of the last century, i.e., two decades before the research the authors of this review had been started. Interest in the possibility of reversible inhibition of the functional activity of some brain structures using ultrasound was aroused by a number of practical tasks in medicine. For example, it could provide high accuracy in irradiation brain structures by powerful focused ultrasound during ultrasonic neurosurgical operations by means of a preliminary action of deliberately nondestructive ultrasonic doses that could result in reversible changes in these structures. This would simplify complicated and time-consuming methods based on the finding of intracranial and cerebral marks. According to Lele [1], the problem of obtaining reversible changes in brain structures is crucial for implementation of focused ultrasound in clinical neurosurgery. Using ultrasound would also be extremely useful for studying the functions of different parts of the brain and structural and functional relationships in the central nervous system.

W. Fry et al. were among the first researchers to study the effect of ultrasound on the conduction of nerve fibers [2]. The action of ultrasound with an intensity of 35 W/cm^2 (frequency of 0.98 MHz) on the conductivity of the ventral nerve cord of the lobster caused the effect of reversible inhibition. The frequency of spike potentials first increased and then decreased, and within about 40 s after the action, large potentials completely disappeared. Twenty-five seconds after turning off the ultrasound, they reappeared and gradually increased. Then, 40 s after turning off the ultrasound, they reached the initial amplitude and frequency.

These studies were further developed in the same laboratory [3–6]. In particular, it was shown [4] that the effect of focused ultrasound of relatively high-intensity on the lateral geniculate nucleus of a cat's brain causes reversible inhibition of electrical responses in the visual cortex to light stimulation of the eyes. Complete restoration of visual function occurred within 30 min after the irradiation. No morphological changes in the irradiated nerve tissue were observed.

The reversible effect of the focused ultrasound with a frequency of 2.7 MHz on the Edinger–Westphal nucleus, the activity of which is related to the regulation of dilation and contraction of the pupil, was studied in the experiments on cats [7]. Destruction or stimulation of these nuclei leads to a distinct pupillary reaction. Irradiation was performed by a sequence of pulses with an intensity at the focus of 1700 W/cm^2, duration of 0.14 s, and frequency of ones 1/3 Hz; the number of pulses ranged from 1 to 13. It was found that, in several experiments, pupillary dilation and contraction were not accompanied by histological changes in the irradiated tissue.

P.P. Lele [8] studied the effect of focused ultrasound with a frequency of 0.6–2.7 MHz on the conductivity of the peripheral nerves in cats, monkeys, and humans. It was found that the ultrasonic dose required for blocking the conductivity of the nerve decreased with an increase in the environmental temperature in the irradiated region. According to Lele, all physiological effects associated with the effect of ultrasound on the nerve fibers can be reproduced using dosed application of heat to certain regions of the nerves. That is, Lele suggests that the effect that ultrasound has on the conductivity of nerve fibers has a thermal nature.

When affecting the sciatic frog nerve by focused ultrasound in a number of particular modes, the thin nerve fibers can be blocked without changing the conductivity of the thick fibers [9, 10]. The peculiarity of this method was that the nerve was placed into a rubber block. As a result, the temperature of the nerve increased significantly more compared to the effect of ultrasound *in vivo*, as the absorption coefficient of ultrasound in rubber is very high.

According to P.O. Makarov et al. [11–13], when applied to a nerve trunk, ultrasound does not cause the spreading of excitation in the nerve or in individual nerve fibers, although it changes some of their functional properties. At the moment, the possibility of activation of free nerve endings, single A–delta nerve fibers, and C–fibers using focused ultrasound has been proven experimentally [14–25]; however, neither local impulse activity nor propagating excitation have been achieved by means of direct action of ultrasound on brain structures.

Theoretical study by W.J. Fry [26] is interesting from this point of view. In this study, a method of electrical stimulation of the neural tissue in the deep structures of the brain without placing electrodes inside the brain is suggested. The essence of the method is based on the interaction of an alternating electric field applied to the brain from outside and the acoustic field generated by focused ultrasound localized in the site of stimulation. In the simplest case, the electric and acoustic fields have the same frequency. Spreading of the acoustic oscillations in tissue is accompanied by temperature changes. Since the electrical conductivity of the tissue depends on the temperature, the acoustic field causes periodic changes in these parameters with maximal variations in the focal region. Tissues expand when heated, and contract when cooled. As a result,