Effect of Ultrasound Stimulation on Excised Brain Tissue Impedance

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ULTRASOUND (US) may allow new methods for noninvasive brain stimulation or neuromodulation, with deeper penetration and sharper focus than TMS (Transcranial Magnetic Stimulation) or tDCS (Transcranial Direct Current Stimulation). Noninvasive neuromodulation could help treat many brain disorders. Recent studies have found US can stimulate the brain in mice: short pulses aimed at motor cortex can evoke muscle twitch [1]

The mechanism of US stimulation is unknown. Cavitation is supported by evidence that low frequency US stimulates more easily than high frequency [2]. Evidence against cavitation is given by US stimulation of retina at 43 MHz [3] and by US simulation occurring without blood-brain barrier opening [1]. Temperature rise is not likely the mechanism [1], [2].

US stimulation may share a mechanism with sonophoresis or sonoporation, which lower skin and membrane resistance. Stimulation could also be explained by the bilayer sonophore (BLS) hypothesis, which proposes that the negative pressure phase of a US wave can separate the leaflets of lipid membranes [4]. This putative effect would lower membrane capacitance. A similar effect has been proposed for the interaction of tDCS with US stimulation, with tDCS polarizing tissue and US changing capacitance to create a localized displacement current which stimulates brain [5].

To look for evidence of these effects we measured brain tissue impedance while applying pulses of US. We used fresh nonliving tissue to avoid indirect biological effects. We also avoided the known acoustoelectric effect on tissue resistance [6]. We measured impedance through a 3x5x10mm sample of rat brain in Ringer's solution with a four-electrode setup. US was applied perpendicular to the current path. The electrodes were not in the US beam. We used three paradigms: a single US pulse with AC and with DC current, and repeated US pulses with a DC current. The single-pulse AC test measured tissue impedance across a range of electrical frequencies. The two DC tests were designed to charge up tissue's large low-frequency capacitance, then look for a voltage response from a capacitance change. Both single-pulse experiments used 45 W/cm^2 US in continuous pulses 10ms to 1s long. The repeated-pulse experiment used 9 W/cm^2 US, chopped at 1 kHz 50% duty. All experiments were done with 200 kHz and 1 MHz US. The DC current was 10 µA applied for 2s to 20s, the AC current was 1 µA at 10 Hz to 100 kHz.

The AC experiment showed small changes in impedance across the frequency range. The DC experiment applying a 45 W/cm^2 1s pulse of 200 kHz US to DC-polarized tissue generated up to 500 µV, with polarity dependent on the DC current, and a control experiment with US aimed away from tissue sample made only a small artifact. To see if these effects were thermal, we simultaneously measured tissue temperature. The temperature rose by several °C during the 1s US pulses, then returned to baseline over ~10s. The AC and DC impedance changes returned to baseline nearly the same rate as temperature. This suggests the impedance change was caused purely by heating, and therefore not likely related to ultrasound stimulation.

We conclude that if sonoporation or membrane distortion is involved in ultrasound stimulation, it does not strongly affect bulk tissue resistance. However, even a very small conductance change could affect neurons by calcium influx at the synapse.

To look further for interaction of tDCS with ultrasound stimulation, we applied both to mouse motor cortex. We found tDCS can enhance or suppress a forepaw twitch driven by an ultrasound pulse. It is unclear if this effect involves a physical interaction, or simply the independent action of tDCS and ultrasound on cortex.

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