Investigating the Bioenergetic and Biophysical Effect of Ultrasound on Neural Mitochondrial Activity

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Ultrasound neuromodulation is an emerging technique in the field of neuroengineering which uses acoustic pressure waves to control neural activity. Ultrasound stimulation is unique in its ability to pass through the cranium and deep tissue noninvasively, showing promise in clinical applications as a therapy for neurodegenerative diseases. Despite studies implicating mitochondria in the neural response to ultrasound, the role of mitochondrial activity in ultrasound neuromodulation have not been fully explored. Therefore, there is a critical need to determine the bioenergetic effects and biophysical mechanisms of ultrasound on neuronal mitochondria. The implication of a mitochondrial transduction pathway in ultrasound neuromodulation would broaden understanding of both the neuron's response to mechanical stimulation and neural activity energetics, further enabling its use as an investigative tool and expansion of its clinical potential. First, an in vitro confocal imaging protocol was developed to quantify bioenergetic activity using the mitochondrial inner membrane-targeted voltage dye TMRM. A specimen setup was designed to enable simultaneous imaging and ultrasound stimulation. Then, the dynamics of the voltage gradient driving ATP production under spontaneous and pulsed ultrasound conditions were compared to assess the effects of stimulation. Finally, the biophysical interaction between ultrasound and the mitochondrial membrane was modeled in silico via molecular dynamics simulations, and membrane voltage changes were derived from the simulated deformations to be validated against empirical data. These results evaluate an alternate pathway for ultrasound transduction via the mitochondria and the possibility for bioenergetic uses of ultrasound stimulation.