NEUROSCIENCE

Pressuring neurons into action

An alternative to optogenetics, sonogenetics uses ultrasound to mechanically stimulate neurons.

Non-invasive optogenetic manipulation of neurons requires the delivery of light to the cells and tissues of interest, which can be tricky in deep tissue or in non-transparent organisms. Sreekanth Chalasani and his colleagues at the Salk Institute in La Jolla, California, have applied an alternative method in the worm *Caenorhabditis elegans*: the use of ultrasound to stimulate specific neurons, which they call sonogenetics.

Ultrasound has been used in vertebrates to stimulate neurons, but without the possibility of targeting specific cells. In the worms, Chalasani and colleagues observed behavioral responses to single ultrasound pulses, depending on the pressure of the ultrasound. However, these responses occurred only when the researchers added tiny bubbles that surrounded the worms. These microbubbles amplified the ultrasound, resulting in a mechanical stimulus.

Although the mechanism of neural stimulation in vertebrates is unclear, Chalasani and his team found that the mechanosensory channel formed by TRP-4 mediated the behavioral response in the worms. Conveniently, TRP-4 is expressed in very few neurons in *C. elegans*. When TRP-4 was ectopically expressed in sensory (or more internally localized) neurons, the cells were sensitized to ultrasound stimulation, eliciting neural activity and behavioral responses at the whole-animal level. For example, TRP-4 expressed in nociceptive neurons induced reversal behavior upon ultrasound application. In addition, the authors assigned a function in reversal suppression to a thus far poorly characterized neuron called PVD.

Sonogenetic activation of neurons does not require direct contact of TRP-4–expressing neurons with microbubbles, as internally localized neurons could be manipulated by this method. As ultrasound can penetrate the skull in vertebrates, it will be interesting to see whether sonogenetics can be adapted for targeted neural manipulation in other organisms. This would potentially require the injection of microbubbles into the brain and the identification of suitable mechanosensitive receptors. Ideally these receptors would not normally be expressed in the brain areas exposed to the ultrasound, as this would increase the specificity of the manipulation.

Many tools for the analysis and manipulation of neural function are dependent on optical means, but cross-talk between the tools' spectral sensitivities can complicate experiments. Thus, orthogonal methods such as sonogenetics could come in handy.

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RESEARCH PAPERS

Ibsen, S. *et al*. Sonogenetics is a non-invasive approach to activating neurons in *Caenorhabditis elegans*. *Nat. Commun.* **6**, 8264 (2015).