This Week in The Journal

Ultrasound Activates Mechanosensitive Channels

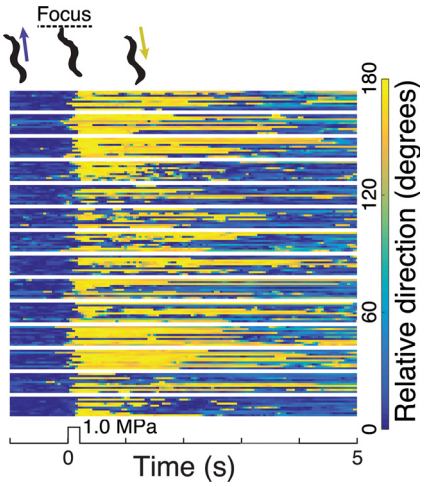
Jan Kubanek, Poojan Shukla, Alakananda Das, Stephen A. Baccus, and Miriam B. Goodman

(see pages 3081–3091)

Ultrasound was first shown to alter neural activity in peripheral nerves nearly a century ago, and its ability to elicit action potentials in the CNS was demonstrated in the last decade. Still, how ultrasound modulates neural activity remains poorly understood. At high intensities, ultrasound waves heat tissue enough to kill cells, but at the intensities used for neuromodulation, heating is minimal. Therefore, ultrasound is thought to influence neural activity through its mechanical effects. These include vibration of the cell membrane at the carrier frequency and the so-called acoustic radiation force: a steady-state force produced by the advancing wavefront when it reaches an interface between two materials that have different sound-scattering properties (Naor et al. 2016 J Neural Eng 13:031003).

To investigate the possible mechanisms of ultrasonic neuromodulation, Kubanek et al. examined how application of pulsed, focused ultrasound affected the behavior of *Caenorhabditis elegans*—animals that are exceptionally sensitive to both thermal and mechanical stimuli. When an ultrasound beam was focused on the head of a crawling wild-type worm, the worm reversed direction. Notably, mutant worms that were unresponsive to small changes in temperature still responded like wild-type worms to pulsed ultrasound. In contrast, mutant worms that lacked a specific subunit of mechanosensitive ion channels (MEC-4)—or neurons that express these channels—showed no behavioral response to ultrasound. Importantly, a simulation of the propagating ultrasound field suggested it produced an acoustic radiation force large enough to activate the mechanosensory neurons.

These results indicate that mechanical, rather than thermal effects underlie the ability of ultrasound waves to modulate behavior in *C. elegans*, and that this effect requires activation of MEC-4-expressing mechanosensory neurons. The authors suggest that deformation of the plasma membrane by acoustic radiation force activates MEC-4 channels. Notably, several voltage-gated sodium and potassium channels expressed in mammals are mechanically sensitive (Tyler 2012 Nat Rev Neurosci 13: 867). Therefore, activation of these channels might underlie ultrasound-mediated modulation of neurons in the mammalian brain. Future work might attempt to identify or engineer channels that are unusually sensitive to ultrasound stimulation. Expressing such channels in specific neuronal types might then allow researchers to activate or suppress those neurons noninvasively.



Delivery of an ultrasound pulse to the head of advancing nematodes caused the animals to reverse direction. Responses of 14 worms; 10 trials/animal are shown. See Kubanek et al. for details.

Amygdala Activity Maintains Stimulus Salience

Auntora Sengupta, Joanna O.Y. Yau, Philip Jean-Richard Dit Bressel1, Yu Liu, E. Zayra Millan, et al.

(see pages 3001–3012)

When an animal encounters a novel stimulus, it attends to the stimulus to assess its significance. If nothing notable occurs in conjunction with the stimulus, the animal's response weakens, and with repeated encounters, the stimulus is eventually ignored. But if the novel stimulus is repeatedly followed by a reward or punishment, the stimulus retains its salience and acquires the ability to elicit a conditioned response. How rewarding or aversive stimuli influence the salience of a preceding predictive stimulus is unknown, but Sengupta et al. provide evidence that activity in the basolateral amygdala (BLA) is required.

The authors trained rats to associate a visual or auditory cue [conditioned stimulus (CS)] with delivery of a foot shock. Shock delivery caused rats to refrain temporarily from pressing a lever for food; and after training, presentation of the CS alone suppressed feeding. The shock also activated neurons in the BLA, and if these neurons were inhibited during shock delivery (by activating an inhibitory opsin expressed in the neurons), the CS no longer suppressed feeding. When BLA neurons were not inhibited during conditioning, but were inhibited at the time a shock was expected during extinction training, extinction of the conditioned response was accelerated, and the rats were slower to reacquire conditioned responses when cues were again followed by shock. The authors also subjected rats to safety training, in which one stimulus (X) was presented along with an additional stimulus (A or B), and shock was delivered only after AX occurred. Such training normally causes B to become a safety signal that suppresses fear responses to X. But if BLA neurons were inhibited immediately after the presentation of BX, safety learning was slowed.

According to theoretical models of learning, this pattern of results—along with results from additional control experiments—suggests that activation of BLA neurons during delivery or omission of an expected shock maintains CS salience. When BLA neurons are inhibited, the CS loses its ability to evoke a conditioned response even during subsequent training. Future work should identify the synaptic targets of neurons activated during the shock and elucidate how these neurons maintain CS salience.

This Week in The Journal was written by Teresa Esch, Ph.D.