MEETING BRIEFS

Neuroscience Fantasia in an Appropriate Setting

Anaheim, California–Last week 14,000 neuroscientists converged on the home of Disneyland for a fantasia of their own: the 22nd annual meeting of the Society for Neuroscience. The neuroscientists' gathering was an assault on the mind and senses, with themes ranging from molecular to cognitive and from clinical to basic. Here is the first installment of our meeting coverage–another will follow next week.

Huntington's Marker

On the first day of the meeting, neurologist Walter Koroshetz of Massachusetts General Hospital announced a landmark advance in research on Huntington's disease: Neurons in the brain region affected by Huntington's produce excess lactic acid. The finding provides a long-sought marker to help gauge the success of experimental treatments. It also offers clues about the mechanism of the disease by linking several far-flung observations together in a coherent model.

Koroshetz and his colleague Bruce Jenkins used a modified form of magnetic resonance imaging on Huntington's patients to detect the lactic acid buildup. Lactic acid is a sign that the neurons have switched from the normal production of energy in the mitochondria to glycolosis, a much less efficient method. "The lactic acid is not toxic," says Koroshetz, but it is a "red flag" that the mitochondria in affected neurons may be defective. And that would place the neurons under potentially deadly metabolic stress. Evidence bolstering that view comes from Flint Beal, also of Massachusetts General, who found that mitochondrial poisons cause rats to develop Huntington's-like brain damage.

The new findings dovetail nicely with evidence suggesting that the neurons that die in Huntington's disease are "excited to death" by the neurotransmitter glutamate. While this excitotoxicity model has gained a lot of support, it begs the question of why excitation (which, after all, is a normal function of neurons) is deadly for these particular cells. Excitation places a heavy energy demand on neurons, and the work by Koroshetz and his colleagues suggests that the neurons affected by Huntington's disease run out of gas and die.

The notion that faulty mitochondria are what makes the neurons vulnerable to excitotoxicity is "an extremely significant development" says Columbia University Huntington's disease researcher Nancy Wexler. "We never thought about that kind of interaction before," she adds. "It's like you've been groping along...and someone just handed you a new pair of glasses."

Although researchers don't know why Huntington's neurons have abnormal metabolism, this finding gives them a new strategy in their search for a treatment. They are testing drugs that might help boost mitochondrial function, Koroshetz said, and are also using lactic acid as a marker for determining the drugs' effectiveness.

Tuning Our Hearing

The hair cells of our inner ear convert vibrations to electrical signals by means of a biological Rube Goldberg machine that's something like a stretchy rubber band pulling open a trap door. The "rubber bands" are fine fibers called tip links; the tip links connect the tips of hair-like protrusions called stereocilia that form bundles at the ends of the hair cells. The "trap doors" are channels that let positively charged ions flow into the hair cell, initiating an electrical signal that is transmitted to the brain. The whole process is activated when a vibration comes along and deflects the cilia, putting enough tension on the tip links to pull the channels open.

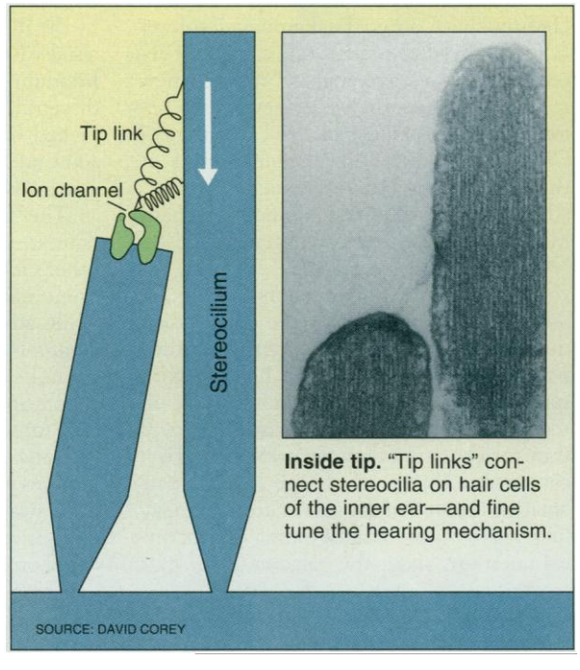
For this system to work, there must be a means of maintaining the right tension in the tip links, so the slightest tug will open the ion channel, and a tiny bit of relaxation will let it close. Researchers in David Corey's lab at Massachusetts General Hospital in Boston, and in Jim Hudspeth's lab at the University of Texas Southwestern Medical Center in Dallas think they have found the tension mechanism, in the form of a tiny molecular motor that moves the anchor-point of the tip link up and down the neighboring cilia.

Several years ago, Hudspeth and Jonathon Howard, then at the University of California, San Francisco, found that when they deflected the cilia and held them in that position, the tension in the stretched tip links loosened over time. That suggested that something was slipping. And if some part of the tip link could slip, that meant there must be a means of restoring the tension, something like retuning a slack guitar string. But what does the retuning? Howard and Hudspeth suggested that there might be a "motor" that pulls on one end of the tip link, just enough to keep it taut.

At the neuroscience meeting, John Assad, a former student with Corey, presented experiments in which he tested Howard and Hudspeth's model and showed that there is in fact a motor that sets the tip-link tension. Assad's results didn't locate the motor, but Gordon Shepherd, a graduate student with Corey, has now found a likely candidate. In electron micrographs, Shepherd sees a dark spot where each tip link inserts into the neighboring cilium. If cilia are deflected in a way that stretches the tip links, the dark spots seem to slide down the cilia, as if pulled down by the increased tension. If the cilia are moved in a way that loosens the tip links, the dark spots climb up the cilia, as if to take up the slack.

The precise molecular identity of the motor is not yet known, but one likely candidate is myosin, a molecule involved in processes such as muscle contraction and other cell movements. Myosin climbs in a ratchet-like way along actin fibers, and the hair-cell cilia are loaded with actin fibers on which myosin can climb. Hudspeth and postdoc Peter Gillespie recently showed that ATP analogs that block the movement of myosin along actin also block tension adjustments in the tip links, and Gillespie reported at the meeting that antibodies to myosin react with a protein from the cilia tips, providing further evidence that myosin is indeed the motor.

–Marcia Barinaga



Inside tip. "Tip links" connect stereocilia on hair cells of the inner ear—and fine tune the hearing mechanism.

PHOTO: GORDON SHEPHERD ILLUSTRATION: H. BISHOP