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RESEARCH NEWS

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Studies of Clumsy Flies Yield Molecule Important in Balance, Hearing

Researchers studying uncoordinated fruit flies have identified a central component of the sensory machinery that underlies balance, touch and hearing. The discovery helps explain how mechanical sound waves are converted into nerve impulses a medically important question since nearly 30 million people suffer from hearing loss due to defects in this sensory machinery.

In an article published in the March 24, 2000, issue of the journal *Science,* the researchers reported experiments in which they precisely twitched the microscopic bristles of uncoordinated mutant flies and measured the ensuing electrical activity. The scientists identified a molecule called an ion channel, which is somehow pried open when a bristle is deflected. When the channel opens, potassium and sodium flow into a neuron, causing an electrical "depolarization" that triggers a nerve impulse. Ion channels are typically large, teepee-shaped proteins that nestle in the cell membrane and control the passage of ions into the cell.

"Previous researchers studying sensory hair cells in the ear developed a very powerful and elegant model of how mechanoreception might work," said Charles Zuker, an HHMI investigator at the University of California, San Diego. "In this model, there is a channel in the sensory cell membrane that opens when a mechanical stimulus impinges on it creating a near-instantaneous neural signal. However, these channels are so rare in each cell that they had never been isolated."

In an effort to pinpoint such channels, Zuker's postdoctoral fellow Richard Walker set out to study mutant fruit flies that were defective in mechanoreception. The mutants had been isolated in earlier studies by another of Zuker's postdoctoral fellows, Maurice Kernan.

"These mutant flies have virtually no sense of balance, so they just fall over when they try to walk," said Walker. "They also frequently cross their legs, which is something normal flies never do."

Using a measurement technique developed by Kernan, Walker first snipped off the tip of a fly bristle, which is about a hundredth the diameter of a human hair. He then slipped a superthin fluid-filled hollow glass pipette over the bristle.

By precisely moving the pipette, he found that he could bend the bristle. Since both the pipette and the hollow bristle were filled with liquid, Walker could measure the electrical current transmitted through the bristle from the fly neuron to which it attached.

Such studies coupled with genetic analyses revealed that several of the flies shared mutations in a particular gene, which Zuker and his colleagues called *nompC*, for "no mechanoreceptor potential-C." The mutant flies either lacked the transduction current or showed currents that indicated rapid adaptation to mechanical stimuli.

"We knew that these two phenotypes had to occur in the same gene, so it seemed very likely that this gene was critically involved in the transduction process," said Walker.

When the scientists isolated the *nompC* gene and analyzed its structure and function, they discovered that it closely resembled genes for other ion channels in flies and vertebrates, including humans.

Aarron Willingham, a graduate student in Zuker's laboratory, then explored whether a similar channel could be found in the roundworm, *C. elegans,* which had been used in some previous studies of mechanoreception. Willingham attached a fluorescent reporter gene to the worm homolog of the *nompC* gene and inserted it into the worms. The experiments indicated that the worm *nompC* gene was specifically expressed in the neurons that were the worm counterparts of the fly mechanosensory neurons.

"Taken together with the earlier findings that the responses of fly bristles are very similar to those of human hair cells, the discovery of *nompC*'s role is likely to impact studies of mechanoreception in other systems, including vertebrate hair cells," said Zuker.

"Since sensorineural hearing loss is such a major medical problem, any advance towards understanding even the most fundamental features of the mechanosensory system can have a significant impact in the development of new therapies," he said.