Sensory Transduction: Confusing the Senses

Two new studies in the fruit fly Drosophila demonstrate unexpected molecular, and mechanistic, overlaps between the different senses. In the centre stand two long-established families of sensory proteins — rhodopsins and TRP channels.

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Be it the infra-red sensitive organ of a highly poisonous pit viper or an electro-receptor in the skin of a weakly electric fish, the gating (i.e. the opening and closing) of specialized ion channels, which transduce the stimulus energy into a membrane electrical response, is the unifying act of all sensation. Most fundamentally, however — and irrespective of the specific sense to which it contributes — the gating of a sensory transducer channel is a mechanical act. The easiest way to bring it about is thus to directly use the force provided by a mechanical stimulus. Such a direct, mechanical gating is widely considered to be the hallmark of the mechanical senses, that is, those that mediate touch, hearing, balance and proprioception. Emphasising the key role that transducers play within the process of sensation, the particular mode of transducer gating has even been used to define one of the major division lines in sensory biology, separating direct (mechanically gated) systems from indirect, second-messenger-dependent ones (which mediate the senses of sight, smell and taste). Two recent studies, conducted on the ubiquitous fruit fly Drosophila melanogaster, have now blurred the boundaries between these two realms and have shaken up a textbook wisdom that had almost seemed to be set in stone [1,2].

In the Drosophila eye, the chain of molecular events that leads from the absorption of a photon to the opening of transducer channels in the photoreceptor cell membrane has been the object of intensive research for more than three decades (see [3] for a recent review). In a nutshell, it comprises the conversion of the photosensitive pigment rhodopsin to metarhodopsin, which activates a coupled G protein. The G-protein activation, in turn, leads to phospholipase C (PLC)-mediated hydrolysis of phosphatidylinositol 4,5-biphosphate (PIP$_2$) into soluble inositol 1,4,5-triphosphate (IP$_3$), membrane-bound diacylglycerol (DAG) and a single proton. As the ultimate result of this complex signalling cascade, transducer channels — formed by the transient receptor potential (TRP) channels TRP and TRPL — will open and produce the photoreceptor potential. Just how exactly this most crucial step of the phototransduction cascade, namely the gating of the actual transducer channels, is brought about, has remained unclear.

In an attempt to close the mechanistic gap between the hydrolysis of PIP$_2$ and the gating of TRP/TRPL, Hardie and Franze [1] have now used atomic force microscopy (AFM) to scan the photoreceptor membrane for light-induced mechanical forces that might directly result in, or contribute to, the gating of the transducers. Their experiments drew on previous evidence that had linked PIP$_2$ depletion to both changes in membrane properties and TRP/TRPL activation [4,5]. With their unconventional approach, Hardie and Franze [1] may have indeed found the missing link in the Drosophila phototransduction chain. Their results suggest that the cleavage of the membrane-bound PIP$_2$ changes the force balance of the photoreceptor membrane and thereby leads to rapid membrane contractions, which (together with the released proton) directly contribute to transducer gating. In this scenario, phototransduction in Drosophila would actually represent a ‘direct’, mechanically gated and pH-sensitive transducer system placed downstream from the photoreceptor.
of an ‘indirect’ (second-messenger-dependent) signalling cascade. This functional assembly may violate some long-held ‘truths’ of sensory biology, yet at least it shows that evolution, by construction rather callous agent, occasionally has acted as a humorous reviewer of some of our most cherished textbook certainties.

A second, mirror-symmetrical and congenial finding, is reported by Senthilan et al. [2]. In a targeted gene expression study the authors found various components of the phototransduction chain to be expressed in one of today’s major mechanosensory model organs, the fly’s antennal ear. This list of visual ‘stray proteins’ includes two G-protein subunits, as well as PLC, TRP, TRPL, protein kinase C (encoded by inaC), arrestin 2, the scaffolding protein INAD and four of the fly’s seven rhodopsins (Rhs)! Loss-of-function mutations in the genes encoding these proteins have long been known to result in blindness or severe visual impairment, but Senthilan et al. [2] now demonstrate that, for many of them, loss of gene function also results in severe hearing disorders. Double mutants for Rh5 and Rh6, for example, display an almost complete loss of auditory amplification and a considerable elevation of the thresholds for sound-evoked nerve responses. Interestingly, the mutant phenotypes of four visual transduction cascade mutants (arr2, inaD, Rh5, Rh6) are very similar: in each case, a reduction of sound-evoked nerve responses is accompanied by an almost complete abolition of the transducer-based, nonlinear feedback amplification, which boosts hearing in flies [6]. This phenotypic similarity suggests that the corresponding proteins form a functional unit in the flies’ ears just as they do in their eyes. The dual nature of the mutant phenotypes, affecting both mechanical [6,7] and electrical responses, strongly points to a contribution to the mechanotransduction process proper. This interpretation is further supported by the striking similarity with the phenotype that was previously reported for a loss-of-function mutation for the auditory transducer channel candidate NonpC (TRPN1) [8,9]. Mimicking the phenotype of nonpC null alleles, the antennal ears of Rh5,Rh6 double mutant flies lose the mechanical signatures of auditory transducer gating, i.e. the gating compliances [7].

Most notably, rhodopsins have also been proposed to act as a class of light-independent, G-protein-coupled receptors in a thermosensory (!) signalling cascade upstream of yet another TRP channel, namely TRPA1 [10]. Although their relative functional placements, and specific interactions, within the fly’s ear still remain to be uncovered, it seems that the interplay between rhodopsin-dependent signalling proteins and TRP channels is an ancient feature in the evolution of sensory receptor cells across the different modalities (Figure 1). Whether it is about to see the light, feel the heat or just hear the sound of the world, it seems that evolution prefers recycling and reshuffling the same old building blocks, rather than creating each new sense from scratch.

References