New and Notable

Frequency Tuning in the Turtle's Cochlea: Who Sets the Stage?

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The cochlea of higher vertebrates is said to be tuned. That is to say that when an animal is exposed to a pure tone, a subpopulation of the cochlea's sensory cells, the hair cells, is maximally stimulated (Dallos, 1992). In mammals, tuning is due to the mechanical properties of the cochlea. Local refinement of this tuning is attributed to the mechanical action of outer hair cells (Dallos, 1992). In contrast to mammals, the frequency selectivity of individual hair cells in the turtle is largely due to the interactions between several of the cell's ionic conductances. When these cells are appropriately stimulated their membrane potential resonates with a characteristic frequency that depends on the cells' location along the cochlea. In other words, these cells are electrically tuned. As in mammals, the turtle's cochlea is tonotopically organized. The hair cells are arranged in ~100 rows that are distributed along the long axis of the cochlea. The frequency selectivity of the hair cells varies nearly exponentially with distance along the organ, with cells close to the base responding maximally to 600 Hz, and those near the apex responding to 40 Hz.

How is this cochlear map of frequencies generated during development? How can cells be informed of their position along the cochlea for them to be able to regulate the frequency to which they are tuned? This is a well-known problem in developmental biology, and one whose solution has often been attributed to the action of morphogens, chemicals whose concentration can regulate particular cellular properties in a specific manner (Wolpert, 1969). Morphogens are thought to originate from a source at which they are produced and to disappear into a sink, where they are degraded. This arrangement sets a continuous chemical gradient along a specific dimension of the organ. A cell is therefore informed of its position by the presence of a certain concentration of the morphogen at its location. Could such a chemical gradient set the stage for tonotopic organization in the auditory system? Yes, suggest Yuh-Cherng Wu and Robert Fettiplace (1996) from the University of Wisconsin at Madison. In an article appearing in this issue, Wu and Fettiplace argue that such a mechanism could account for the spatial map for frequency tuning in the reptilian and avian cochleas.

Evidence for the presence of a morphogen in the cochlea is lacking. How one would go about characterizing this hypothetical substance in the cochlea is also not clear. Even potential candidates for the morphogen role remain to be identified. However, the authors make a strong argument for the plausibility of a morphogen gradient regulation of frequency tuning in the turtle and avian cochleas. In essence, they show that, on the basis of a relatively simple mechanism, a morphogen gradient could quantitatively account for the establishment of the cochlea's frequency map.

The model presented by Wu and Fettiplace focuses on the KCa channels, which are opened by voltage and by the Ca that comes into the hair cell through neighboring voltage-dependent Ca channels. To a first approximation, it is the number and kinetics of these K channels that are responsible for the frequency to which a given cell is tuned. These KCa channels are assumed to be heterotetrameric combinations of two different subunits whose intracellular concentration is a function of the morphogen's concentration reaching the hair cell. Four combinations of subunits would assemble into four types of channels, each with distinct kinetics resembling the four broad categories that have been inferred from single channel recordings. Thus, the authors suggest that by governing the numbers of both subunit types in any given cell, the morphogen can specify the cell's frequency of tuning. However, such simplicity is only apparent: complexity resides in how cells must respond to a certain concentration of morphogen. The authors approach this problem by proposing that three arbitrary parameters are sufficient to describe a cell's response to the gradient. This enables them to account for the necessary expression patterns of KCa subtypes that yield the desired frequency tuning. However, it must be emphasized that other models of KCa channel organization (e.g., the use of two channel subtypes) cannot be reconciled with the observed pattern of tuning, as well as with position-dependent electrophysiological properties that are a direct consequence of KCa kinetics.

The authors' efforts underscore the unusual appeal of this developmental system. In most other cases morphogens act in a way that has been described in a qualitative manner. For instance, it has been shown that the product of the bicoid gene in *Drosophila melanogaster* acts as a concentration-dependent transcriptional activator, to organize the anterior part of the embryo (Driever and Nüsslein-Volhard, 1989; Struhl et al., 1989). However, no morphogen has been shown to account in a precisely quantitative manner for any cellular property. Wu and Fettiplace propose a model of frequency tuning that might, as they recognize, be incorrect in its details. However, they convincingly show how morphogen concentration could precisely determine a particular phenotype of individual hair cells along the morphogen's gradient.

The questions addressed by the authors can be extended to mammals, where properties such as the length of

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stereocilia, the number of afferent synapses, the mechanical properties of the basilar membrane, etc., also vary continuously along the length of the cochlea. The elucidation of the mechanisms that regulate the position specific properties of this organ remains a formidable challenge.

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