Review

Progress in cochlear physiology after Békésy

John J. Guinan Jr. [a,b,∗], Alec Salt [c], Mary Ann Cheatham [d]

[a] Eaton Peabody Laboratories, Dept. of Otolaryngology, Mass. Eye and Ear Infirmary, Boston, MA 02114, USA
[b] Dept. of Otology and Laryngology, Harvard Medical School, Boston, MA 02115, USA
[c] Department of Otolaryngology, Washington University School of Medicine, Box 8115, 660 South Euclid Avenue, St. Louis, MO 63110, USA
[d] The Hugh Knowles Center, Department of Communication Sciences and Disorders, 2240 Campus Drive, Northwestern University, Evanston, IL 60208, USA

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ABSTRACT

In the fifty years since Békésy was awarded the Nobel Prize, cochlear physiology has blossomed. Many topics that are now current are things Békésy could not have imagined. In this review we start by describing progress in understanding the origin of cochlear gross potentials, particularly the cochlear microphonic, an area in which Békésy had extensive experience. We then review progress in areas of cochlear physiology that were mostly unknown to Békésy, including: (1) stereocilia mechano-electrical transduction, force production, and response amplification, (2) outer hair cell (OHC) somatic motility and its molecular basis in prestin, (3) cochlear amplification and related micromechanics, including the evidence that prestin is the main motor for cochlear amplification, (4) the influence of the tectorial membrane, (5) cochlear micro-mechanics and the mechanical drives to inner hair cell stereocilia, (6) otoacoustic emissions, and (7) oli-vocochlear efferents and their influence on cochlear physiology. We then return to a subject that Békésy knew well: cochlear fluids and standing currents, as well as our present understanding of energy depen-dence on the lateral wall of the cochlea. Finally, we touch on cochlear pathologies including noise damage and aging, with an emphasis on where the field might go in the future.

1. Introduction

In celebration of the 50-year jubilee for Georg von Békésy's Nobel Prize we review progress in cochlear physiology with a special view to those areas in which Békésy made important contributions. In order to make this paper understandable to non-experts in the field, we focus on major trends and controversies. This necessitates that important details are omitted. Because it is impossible to reference all of the papers that have been important in producing our current understanding of cochlear physiology, we reference a mix of original papers from the discoverers of phenomena, and more recent papers that provide a variety of relevant references. Although many interesting things have been learned about non-mammalian hearing, we concentrate on mammalian cochlear physiology.

2. The origin of cochlear gross potentials

As Tonndorf (1986) reported, Békésy was employed at the Telephone System Laboratory of the Post Office in Budapest, the best place in Hungary for his experimental endeavors since scientific equipment was available there. Because of the rather primitive understanding of the inner ear at that time, Békésy found it difficult to answer questions from his engineering colleagues about auditory physiology. Fortunately, a supportive environment allowed Békésy to begin the experimental studies that would become his life work.

Békésy's early electrophysiological experiments were designed to pinpoint the origin of the cochlear microphonic (CM). CM was thought by its discovers, Wever and Bray (1930), to be from the auditory nerve. However, at the time that Békésy performed his experiments, it was known that the CM was not coming from the

auditory nerve (Adrian, 1931), and that it disappeared with organ of Corti removal, thereby implicating hair cells in its generation. In spite of the fact that some considered the CM to be an epiphenomenon (Davis, 1949), Békésy wondered what role this gross ac cochlear potential might have in peripheral signal coding. His early observations indicated that the vibratory patterns of the basilar membrane (BM) were complex such that the CM represented an integration of voltages produced along the partition, which complicated their interpretation. Even when Békésy used a sharp needle to set a small section of the partition into motion, there were phase cancellations in CM. A differential electrode technique was introduced by Tasaki et al. (1952) to at least partially deal with these complications.

In order to determine the place of origin of the CM, Békésy described three tissues that an electrode encountered in its traverse of the cochlear partition after entering from scala tympani. The first included the BM, which did not produce potentials and, therefore, acted as a simple electrical resistance. The second included supporting cells like Hensen and Claudius cells that do not generate a first-order CM but appeared to function like batteries with negative resting potentials. Finally, the third group included active cells responsible for the large potentials seen in the scala media (SM). With improved recording technologies Békésy would probably have been able to record from individual hair cells in addition to his observations of the endocochlear potential (EP) and injury potentials as the recording electrode passed through the cochlear partition. The first actual *in vivo* intracellular hair cell recordings were made by Russell and Sellick (1978). These inner hair cell (IHC) recordings from the base of the cochlea were later supplemented by inner and outer hair cell (OHC) measurements from the apex by Dallos et al. (1982).

Békésy's experiments using a vibrating electrode demonstrated that the CM was proportional to BM displacement not velocity. These experimental results foreshadowed the later intracellular work showing that OHCs respond to BM displacement, IHCs to velocity at least at low frequencies. Current thinking suggests that when recorded at the round window, the CM is dominated by receptor currents generated primarily by basal OHCs (Patuzzi et al., 1989) responding to inputs below their characteristic frequency (CF). In other words, the CM recorded from distant electrodes is a passive phenomenon, something that Békésy understood in the 1950s.

3. Stereocilia mechano-electrical transduction (MET) and amplification

Shortly after Békésy received the Nobel Prize in 1961, the first key steps were made in understanding hair cell mechano-electrical transduction (MET). Experiments in the lateral line demonstrated that displacing stereocilia toward the tallest row caused current flow into a hair cell (Flock, 1965). The CM is a gross reflection of these receptor currents, i.e., hair cell MET underlies its generation. Over the past decades much more has been learned about MET in stereocilia, mostly from vestibular and non-mammalian hair cells (Gillespie and Müller, 2009). MET in stereocilia is mediated by connections between adjacent rows of stereocilia called "tip links" (Fig. 1A). Displacing the stereocilia in the excitatory direction pulls on the tip links, thereby increasing open probability, and current flow through the channels (Fig. 1B). From the point of view of a single channel, the action is somewhat like a spring pulling on a door that opens when the tension is sufficient; however, there is not a fixed tension at which the channel opens. Instead the channel opening is probabilistic with open probability increasing as the tension becomes greater. An individual channel rapidly flips between closed and open states, and the tip-link tension controls the proportion of time that the channel is open. The mechanical coupling between the tip-link tension and channel opening is likely
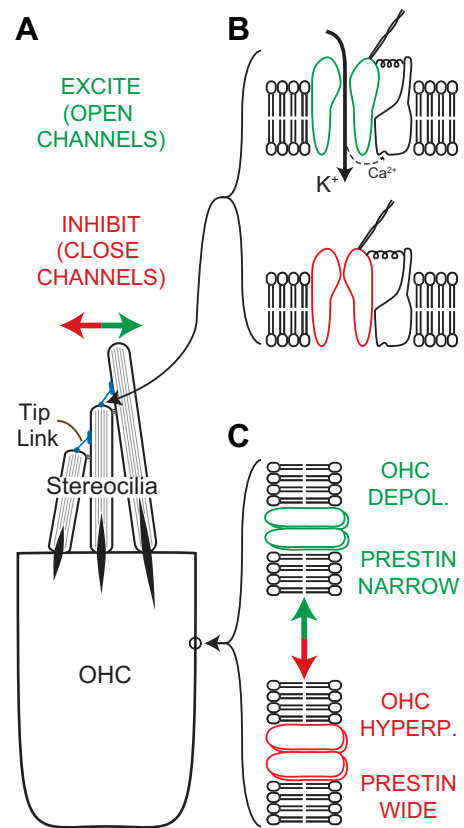

Fig. 1. A schematic of OHC mechano-electrical-transduction (MET) and prestin conformational change. A: Tip links connect the MET apparatus on short stereocilia (expanded in B) with the next taller stereocilia. Circled is a prestin-containing patch of lateral membrane (expanded in C). Deflection toward the tallest stereocilia pulls on the tip links and increases the probability that the channels will open. Deflection toward the smallest stereocilia does the opposite. B: Cartoon of the MET channel protein in the open (green) and closed (red) state. When the channel is open, potassium (K^+) and calcium (Ca^{2+}) ions flow into the OHC. Calcium ions bind to a nearby site, which reduces the open probability, perhaps by relaxing a spring-like element. The binding site is shown here in a second protein molecule, even though the actual configuration remains unknown. The receptor current carried by potassium ions depolarizes the OHC. C-top: OHC depolarization (DEPOL) causes prestin molecules to become narrower resulting in OHC somatic contraction. C-bottom: OHC hyperpolarization (HYPERP) causes prestin molecules to become wider resulting in OHC somatic elongation.

to be bidirectional. If something causes a channel to close, it pulls on the tip link and moves the stereocilia (i.e., if the door is closed it stretches the spring). This is important as it represents a mechanism whereby physiological responses of hair cells can cause mechanical movements.

In the cochlea, the tip links are maintained in a state of tension, so that in the resting state the channel-open probability is not zero. This results in there being a resting current flowing through the hair cells. The resting current allows both increases and decreases in tip-link tension to change current flow through the stereocilia, i.e., hair cell current can be modulated in both directions by sound. The resting operating point of the channel-open probability varies across hair cell types and from base to apex. At the base of the cochlea, ~50% of the MET channels in OHCs appear to be open, which is much larger than the ~11% estimated for OHCs at the apex (Dallos et al., 1982) and for IHCs at all cochlear locations (Russell and Kössl, 1991).

When deflections of the stereocilia cause more MET channels to be open than in the resting state, electrochemical gradients (see below) cause more current to flow into the stereocilia with several