18.0 Auditory Physiology

18.1 Signal Transmission in The Auditory System

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18.1.1 Basic and Clinical Studies of the Auditory System

National Institutes of Health (Grants 5 PO1 NS13126,
5 RO1 NS18682, 5 RO1 NS20322, 5 RO1 NS20269,
5 PO1 NS23734 and 5 T32 NS07047)
Symbion, Inc.

Investigations of signal transmission in the auditory system are carried out in cooperation with the Eaton-Peabody Laboratory for Auditory Physiology at the Massachusetts Eye and Ear Infirmary. The long term objective is to determine the anatomical structures and physiological mechanisms that underlie vertebrate hearing and to apply that knowledge to clinical problems. Studies of cochlear implants in humans are carried out in the Cochlear Implant Laboratory in a joint program with the Massachusetts Eye and Ear Infirmary. The ultimate goal of these devices is to provide speech communication for the deaf by using electric stimulation of intracochlear electrodes to elicit patterns of auditory nerve fiber activity that the brain can learn to interpret.

18.1.2 Signal Transmission in the External and Middle Ear

Kathleen M. Donahue, Darlene R. Ketten, William T. Peake, John J. Rosowski

We seek to relate signal-transmission properties of ears to their structural features. We have been primarily interested in interspecies variations, but in one project we have pursued our goal through anatomical and physiological measurements of intraspecies variations. In the alligator lizard, whose ear we have studied extensively, we have used individuals with a wide range of sizes. The magnitude of the acoustic admittance of the ear at low frequencies correlates well with the size (weight and snout-to-vent length) of the lizard, and with the area of the tympanic membrane. Admittance magnitudes at higher frequencies do not show this close correlation. These results, considered with earlier admittance measurements of the effects of removal of specific structures, suggest that the middle ear structures that control the low-frequency admittances grow with the animal, whereas the structures of the inner ear that are more important at higher frequencies do not.[1] Another suggestion of these results is that larger individuals possess more sensitive hearing, at low frequencies, than smaller lizards.

In another project we have measured acoustic impedances of human cadaver ears to test "normality" of mechanical behavior of these ears.[2] The results show that ears that are kept frozen (when measurements are not being made) show only small alterations over periods of months. The impedance magnitudes are quite similar to those reported for ears of live humans. Thus, with cadaver ears we should be able to make measurements on human ears that are comparable to those we have made on other species.

18.1.3 Cochlear Mechanisms

Dennis M. Freeman, Lawrence S. Frishkopf, Thomas F. Weiss

Manuscripts describing the frequency dependence of synchronization of spikes discharges of cochlear nerve fibers to the phase of a tone have been completed.[3–5] The principal conclusions of these studies are: 1) the cochlea of a variety of vertebrate ears contains lowpass filter processes whose orders sum to at least 4 and which serve to degrade the timing information present in an acoustic stimulus; 2) one such process, which results from the resistance and capacitance of the hair cell membrane, limits the rate at which the membrane potential of a hair cell can change; and 3) the remaining process(es) occur in the transformation of the receptor potential of a hair cell to the spike discharge of a cochlear nerve fiber.

We have designed and built a system to measure submicron motion of inner ear structures in an *in vitro* preparation of the auditory organ of the alligator lizard. The scheme, which is similar to one described in the literature, is to project the microscope image of a structure onto a pair of photodiodes, with the image aligned so that the movement of the object sweeps across the photodiodes. Differential recording of the photodiode currents gives a measure of the displacement of the object across the photodiode surface. By mounting the photodiodes on a device that can be moved a known distance, the apparatus can be calibrated and the displacement of the object relative to the photodiodes can be determined. With this system we have measured displacements as small as 1 nm.

To better understand its structure, we have constructed a three-dimensional scale model of the inner ear of the alligator lizard. We first obtained photomicrographs (at a magnification of 50) of a contiguous series of histological sections of the ear. Tracings of key structures were made from the photographs, and used to cut sheets of balsawood which were then assembled into a three-dimensional model. Flexible polyurethane rubber was used to make a mold for each of three separate parts representing the cochlear duct, auditory nerve, and otic capsule. The molds were then used to cast transparent plastic models of each part. The parts fit together so that the relation between them can be visualized in three dimensions. The model has been used to develop surgical methods and experimental chambers for physiological studies of the alligator lizard ear. It is very useful for anyone interested in learning the anatomy of this ear.

18.1.4 Membrane Properties of Inner-Ear Neurons *In Vitro*

Robin L. Davis

The goal of this work is to characterize the electrophysiological and pharmacological properties of auditory neurons. To this end, a technique has been developed to grow single auditory neurons in tissue culture without the complicating influences of synaptic connections or hormonal regulation. This preparation enables one to ask questions such as:

1. Are there differences in the membrane properties of the two classes of auditory neurons that can be related to the known difference in their discharge patterns?
2. What is the distribution of ionic channel types along the length of these neurons?
3. Are there neurotransmitter-activated channels specific to the peripheral or central projections of these neurons? If so, which transmitters activate these channels?

The goldfish (*Carassius auratus*) was the experimental animal of choice since our laboratory has extensive experience isolating and purifying neuroactive substances released by inner-ear receptor cells in this animal. Our procedure yields two groups of neurons distinguished by their location in the auditory nerve and their axon diameters. One to two weeks after being placed in culture, the cells generate action potentials and sprout processes that can extend for hundreds of microns.[6]

The properties of these neurons will be further evaluated with electrophysiological and pharmacological studies. Preliminary studies have shown that the patch clamp procedure can be successfully implemented to record single channel currents from the growing ends of the neurons as well as from membrane that has been acutely desheathed from its myelin covering. Experiments using the cell-attached configuration of the patch clamp technique have revealed single channel currents with conductances ranging from 16 to 120 pS in solutions that select for K^+, Cl^- or Ba^{++} currents. These conductances and their voltage dependence are being systematically categorized according to ionic specificity as well as position along the length of the neuron. Although this work is in its early stages, the results to date have been extremely encouraging, and it appears that a complete categorization of the channel types is feasible. This will aid considerably in the search for the afferent transmitter substance in the inner ear and will increase our understanding of this important link between the auditory receptors to the CNS.

18.1.5 Stimulus Coding in the Auditory Nerve

Bertrand Delgutte

Masking of tone signals might be caused either by spread of the excitation produced by the masker to the place of the signal along the cochlea, or by suppression of the response to the signal by the masker, or by a combination of the two. To separate these different forms of masking, two types of masked thresholds were measured from auditory nerve fibers in anesthetized cats, using methods mimicking the two-interval, two-alternative forced-choice paradigm of psychophysics: simultaneous masked thresholds, and nonsimultaneous thresholds.[7,8] For measuring simultaneous thresholds, a stimulus consisting of a 1 kHz masker and a tone signal is presented in alternation with the masker alone, and the signal level is adjusted by a PEST procedure until the spike count in response to the two-tone stimulus exceeds the count in response to the masker alone for 75 percent of the presentations. This simultaneous masked threshold reflects the effects of both suppression and spread of excitation. For measuring nonsimultaneous thresholds, the signal alone is presented in alternation with the masker alone, and the signal level is adjusted until the spike counts meet the same probabilistic criterion as in simultaneous masking. The nonsimultaneous threshold must be entirely due to the spread of masker excitation because suppression does not occur when the masker and the signal are not simultaneous. Thus, the difference between simultaneous and nonsimultaneous thresholds gives a measure of the contribution of suppression to masking.

For fibers whose characteristic frequencies (CF) are close to the 1 kHz masker, the two types of masked thresholds are similar, indicating that masking is primarily due to spread of excitation. In contrast, for fibers with CF's either above or below the masker frequency, simultaneous masked thresholds are considerably higher than nonsimultaneous thresholds, suggesting that two-tone rate suppression contributes significantly to masking.

To obtain a general picture of masking for a population of auditory nerve fibers, we determined for each masker and each signal frequency the auditory nerve fibers that had the lowest (or "best") masked thresholds. Profiles of best threshold against signal frequency roughly resemble psychophysical masking patterns, with a maximum near the masker frequency, and a pronounced skew towards high frequencies. Best threshold profiles are more sharply tuned in nonsimultaneous that in simultaneous masking, a phenomenon which is also found in psychophysics. Simultaneous masking patterns for a masker at 80 dB SPL extend considerably more towards high signal frequencies than they do for a 60 dB masker. In particular, for signal frequencies well above the masker, best thresholds increase by 40 to 50 dB for a 20 dB increase in masker level. This supralinear growth of masking is also found in psychophysics, and is called "upward spread of masking." It is much less apparent in nonsimultaneous masking, where the masking seems to grow more linearly. This result suggests that the upward spread of simultaneous masking is due to the rapid growth of suppression rather than to the growth of excitation.

In summary, both two-tone rate suppression and spread of masker excitation contribute to the masking of auditory nerve fiber responses, with suppression being most important for signal frequencies well above the masker frequency. Patterns of best single-fiber masked thresholds against signal frequency resemble psychophysical masking patterns in many respects. Both suppression and spread of excitation are essential to obtain this good correspondence between physiology and behavior.

During the past year a previously-written paper on the physiological basis of intensity discrimination has been published.[9]

18.1.6 Middle Ear Muscle Reflex

John J. Guinan, Jr., Xiao-Dong Pang, Michael P. McCue

We aim to determine the structural and functional basis of the middle ear reflexes. During the past year, we have completed a manuscript which describes changes in the acoustic stapedius reflex produced by brainstem lesions which destroyed selected sets of stapedius motoneurons.[10] The results of this work suggest that inputs from the two cochleas are distributed inhomogeneously across the stapedius motoneuron pool in such a way as to produce a segregation of function, with motoneurons in one brainstem region responding preferentially to contralateral sound and motoneurons in other regions responding preferentially to ipsilateral sound.

We have confirmed and extended this hypothesis by recording from single stapedius motoneurons and determining their responses to sound. During the past year we have completed a paper on the implications of our stapedius recordings with regard to motor control issues.[11] In particular, our results show that the "size principle" a commonly held hypothesis which accounts for the recruitment order of motoneurons innervating a muscle, does not hold for the stapedius muscle.

During the past year, we have completed the data gathering phase of our project in which physiologically characterized stapedius motoneurons are labeled by intracellular injections of the tracer, horseradish-peroxidase (HRP).[12] We now have labeled stapedius motoneurons in each of our five physiological categories. This work shows that stapedius motoneurons with distinctive electrophysiological properties have similar locations in the brainstem with limited overlap between categories. The results are consistent with the idea that the stapedius motoneuron pool is divided into groups which are spatially segregated in the brainstem and receive different patterns of inputs from the two ears.

During the past year, considerable progress has been made on our project to determine the effects of stapedius muscle contractions on the responses of single auditory nerve fibers. It is well known that contractions of the stapedius muscle reduce sound transmission primarily at low sound frequencies. Because of the nonlinear properties of the cochlea, intense sounds at low frequencies are particularly effective in reducing (masking) responses to sounds at higher frequencies. Our experiments have shown that stapedius contractions reduce the masking of high frequency sounds by low frequency sounds. In a typical case, a 20 dB reduction of sound transmission at 0.5 kHz can improve the threshold by 35 dB at 6 kHz. Furthermore, the data show that this effect of stapedius contractions can be fully accounted for by the masking properties of auditory nerve fibers and the attenuation of middle ear transmission produced by the stapedius. Such a reduction of masking is probably one of the most important functions of the stapedius muscle.

With other members of the Eaton-Peabody Laboratory, a paper has been written which describes the acoustic reflex properties of the middle ear muscles and the auditory efferents, and explores the implications these might have for the design of cochlear implants.[13] Also, during the past year a previously submitted paper on asymmetries in the acoustic reflexes of the cat stapedius muscle has been published.[14]

18.1.7 Cochlear Efferent System

John J. Guinan, Jr.

Our aim is to understand the physiological effects produced by medial olivocochlear (MOC) efferents which terminate on outer hair cells. During the past year our efforts have focused on the effects of electrical stimulation of medial olivocochlear efferents on single auditory nerve fibers. The work has included data analysis of previous work done with M.L. Gifford and new experiments to provide data to fill in gaps left by previous experiments. This work has led to three papers, two of which (outlined below) are completed.

In the first set of experiments,[15] we selectively stimulated medial efferents in cats, and determined the changes produced in the firing rates of auditory nerve fibers with sound level as a parameter. Efferent stimulation shifted rate vs. level functions to higher sound levels and depressed the rate in the plateau. The amplitudes of the efferent induced effects were different for auditory nerve fibers with different spontaneous rates (by as much as a factor of three for the plateau depression). The results support several hypotheses: 1) individual crossed and uncrossed MOC fibers produce similar effects; 2) efferents differentially change the information carrying properties of auditory nerve fibers in different spontaneous rate categories; and 3) that the level shifts are produced by MOC efferents acting on outer hair cells to reduce the mechanical stimulus to inner hair cells.

In the second set of experiments,[16] we measured changes in the rate of spontaneous firing (SR) of single auditory nerve fibers in response to the stimulation of medial olivocochlear efferents in cats. Efferent stimulation depressed SR. In most animals, the SR depression increased as auditory nerve fiber sensitivity increased, increased as the original SR decreased and had a maximum at characteristic frequencies (CFs) of about 10 kHz. The data are consistent with the hypotheses 1) that "spontaneous" firing of auditory nerve fibers is reduced by an efferent induced hyperpolarization of outer hair cells which is electrically coupled through the endocochlear potential to inner hair cells and 2) that the reduction is largest at CFs near 10 kHz because this CF region receives the greatest outer hair cell innervation from medial efferents.

During the past year, a paper was written which reviews recent advances in the understanding of the physiology of efferent fibers in the cochlea,[17] and a previously submitted paper was published.[18]

18.1.8 Central Neural Pathways: Evoked Responses

Jennifer R. Melcher, Nelson Y.S. Kiang

We are investigating the brainstem auditory evoked potential (BAEP) which is a time varying potential that can be recorded from electrode pairs on the surface of the head in the 10 msec immediately following the delivery of a punctate acoustic stimulus to the ear of a cat. While it is known that the BAEP is due to currents generated by cells in the auditory nerve and brainstem, exactly which of the numerous cell groups contribute to the BAEP is largely unknown. The goal of this project is to better understand which cells contribute to the BAEP. Our approach is to selectively destroy particular cell groups by injecting kainic acid, a neurotoxin, at discrete locations along the brainstem auditory pathway. The injections result in changes in the BAEP. At the end of each experiment, the brainstem is prepared histologically and the location and number of cells destroyed is determined. The BAEP changes are then compared with the regions of cell destruction.

18.1.9 Cochlear Implants: Current Spread During Electrical Stimulation of the Human Cochlea

Donald K. Eddington, Gary Girzon

The basic function of a cochlear prosthesis is to elicit patterns of activity on the array of surviving auditory nerve fibers by stimulating electrodes that are placed in and/or around the cochlea. By modulating these patterns of neural activity, these devices attempt to present information that the implanted subject can learn to interpret. The spike activity patterns elicited by electrical stimulation depend on several factors: the structure of the cochlea (three-dimensional, electrically heterogeneous), the geometry and placement of the stimulating electrodes, the stimulus waveform, and the distribution of exitable auditory nerve fibers. Understanding how these factors interact to determine the activity patterns is fundamental to designing better devices and to interpreting the results of experiments involving intracochlear stimulation of animal and human subjects. As a first step towards this understanding, the goal of this project is to construct a software model of the cochlea that predicts the patterns of current flow due to the stimulation of arbitrarily placed, intracochlear electrodes.

Last year sections from a human temporal bone were digitized and resistivities were assigned to the major cochlear elements (e.g., bone, nerve, perilymph, endolymph). Finite element techniques were used to convert the anatomical and resistivity data to a set of equations representing a three dimensional mesh of 512 by 512 by 46 nodes. Current sources were defined at nodes representing the positions of the six intracochlear electrodes used in five human subjects implanted at the Massachusetts Eye and Ear Infirmary. The equations were solved and maps of nodal potentials located along the length of the spiraling scala tympani showed a monotonic reduction of potential from the more apically placed current sources toward the base while a potential plateau was observed as one moves from the basal current sources toward the apex. For basal current sources, "bumps" were observed in the potential plateaus between 15 and 20 mm from the base. These nonmonotonicities probably indicate significant current pathways between cochlear turns in addition to the pathway along the scala tympani.

This year we completed the measurement of potentials at unstimulated electrodes made in the initial five human subjects implanted with intracochlear electrodes. These measurements demonstrated the asymmetric potential distributions predicted by the model in all five subjects. The "bumps" predicted by the model were also present in the potential distributions measured during the stimulation of the most basal of the implanted electrodes in all five subjects.

We are now collecting psychophysical measures of current interaction to determine if the pattern of interaction between simultaneously stimulated electrodes will exhibit the same asymmetries as the potential distributions along the scala tympani. Preliminary measurements obtained in two subjects exhibit such an asymmetric distribution of interaction. We are currently collecting these data from the other three subjects.

18.1.10 Cochlear Implants: Electrical Stimulation of the Auditory Nerve

Betrand Delgutte, Scott B.C. Dynes

This project aims at characterizing the patterns of auditory nerve activity produced by electrode configurations similar to those used in cochlear implants, and at identifying physiological limitations on schemes for encoding speech information for electrical stimulation. In these experiments, the activity of auditory nerve fibers in anesthetized cats is recorded in response to electrical currents applied at pairs of electrodes inserted into the cochlea through the round window. Initial efforts focused on measuring the phase locking (or "synchrony") of spikes to electric sinusoidal stimulation. Phase locking is an important property of the response of auditory nerve fibers because it has been suggested that it is essential for discriminating certain vowels, and because, for single channel implants, it is the only way in which information about the stimulus spectrum can be encoded.

A major experimental problem encountered was the stimulus artifact, which arises from currents generated by the stimulus and can result in an artificially elevated measure of phase locking. This problem was essentially eliminated through the development of a special electrode that records differentially between two closely spaced locations, and by the use of an adaptive filter which greatly reduces sinusoidal components at the stimulus frequency in the signal recorded by the microelectrode.

Preliminary results show that phase locking of nerve spikes to sinusoidal stimuli is more pronounced in electrical stimulation than acoustical stimulation, with the synchrony index being larger in electrical stimulation for all frequencies investigated, ranging from approximately 4 kHz to 10 kHz. Also, it seems that the synchronization index reaches its maximum at or very near electric threshold. These results suggest that electrical stimulation can, in principle, mimic some of the temporal fine structure of nerve activity which occurs in the normally functioning ear.

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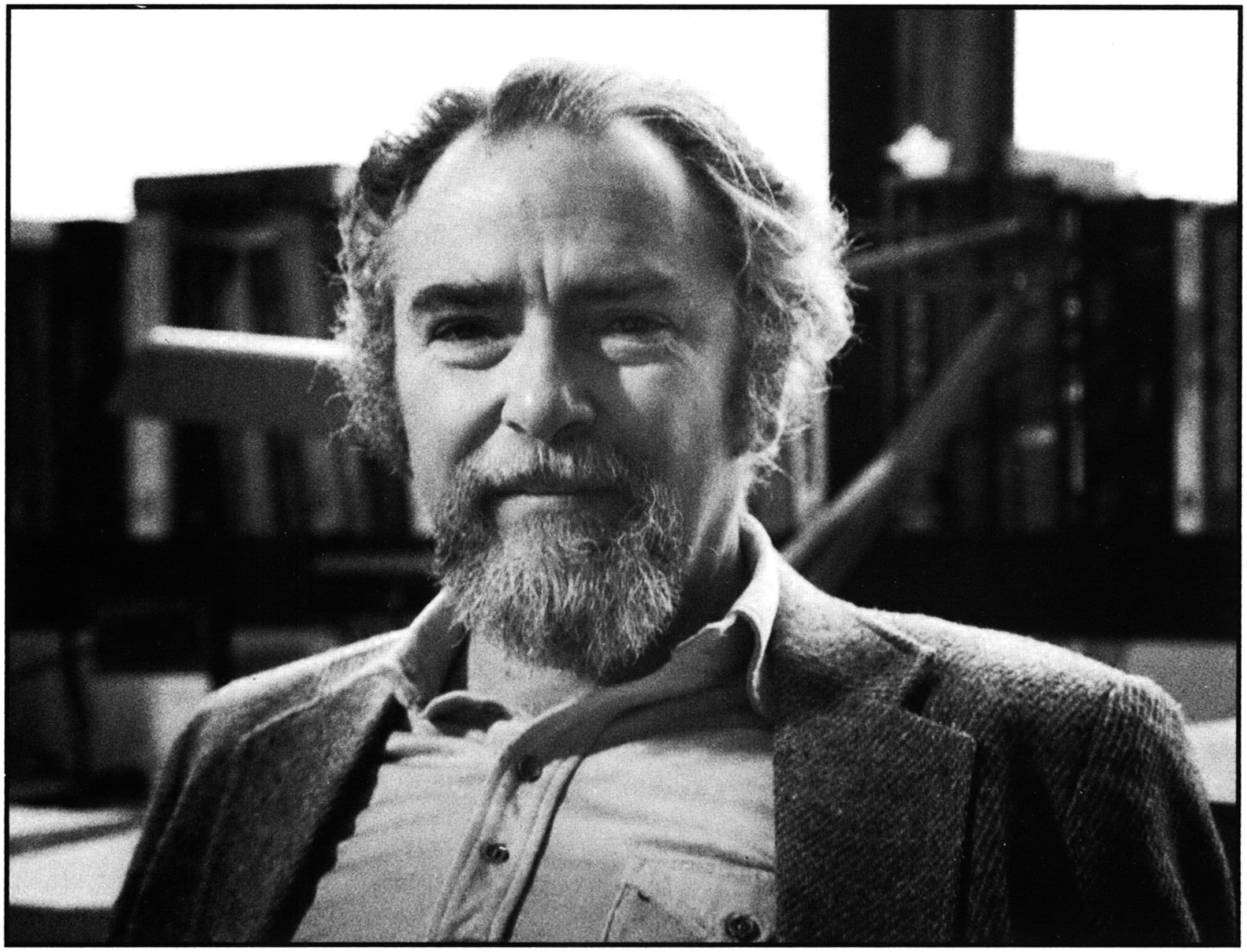

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