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Laurence O. Trussell
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Synaptic Mechanisms in the Auditory System

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Synaptic Mechanisms in the Auditory System

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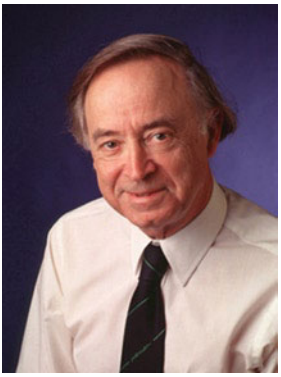

This volume is dedicated to Professor Alan D. Grinnell, whose career has embodied the twin themes that run through the entire book, the auditory system and the physiology of synapses. Alan, along with his advisor Donald Griffin, was the first to make electrophysiological studies in the bat auditory pathway, work he continued as a faculty member at UCLA. Having also trained with Bernard Katz and Ricardo Miledi, Alan has a genuine love for the synapse, which he has expressed in a parallel research career, producing many creative and elegant studies of the physiology of the neuromuscular junction. This was all accomplished by his enormous energy and amazing breadth of knowledge. Indeed, those fortunate enough to work with him know that Alan is a consummate scholar, a deeply inquisitive scientist, and an excellent friend.

Series Preface

The Springer Handbook of Auditory Research presents a series of comprehensive and synthetic reviews of the fundamental topics in modern auditory research. The volumes are aimed at all individuals with interest in hearing research, including advanced graduate students, postdoctoral researchers, and clinical investigators. The volumes are intended to introduce new investigators to important aspects of hearing science and to help established investigators to better understand the fundamental theories and data in fields of hearing that they may not normally follow closely.

Each volume presents a particular topic comprehensively, and each serves as a synthetic overview and guide to the literature. As such, the chapters present neither exhaustive data reviews nor original research that has not yet appeared in peer-reviewed journals. The volumes focus on topics that have developed a solid data and conceptual foundation rather than on those for which a literature is only beginning to develop. New research areas will be covered on a timely basis in the series as they begin to mature.

Each volume in the series consists of a few substantial chapters on a particular topic. In some cases, the topics will be ones of traditional interest for which there is a substantial body of data and theory, such as auditory neuroanatomy (Vol. 1) and neurophysiology (Vol. 2). Other volumes in the series deal with topics that have begun to mature more recently, such as development, plasticity, and computational models of neural processing. In many cases, the series editors are joined by a co-editor having special expertise in the topic of the volume.

Richard R. Fay, Falmouth, MA
Arthur N. Popper, College Park, MD

Volume Preface

This volume illustrates how two time-honored areas of research, auditory systems physiology and synaptic physiology, have come together to generate a new subfield of research, the synaptic mechanisms of auditory coding. That union has generated new insight into systems function, and its success is providing the stimulus for development or application of new techniques and ideas in our field. The topics primarily focus on synapses and ion channels in neurons of the central nervous system, with emphasis on the brainstem, but they also offer an informative look at the first auditory synapse in cochlear hair cells.

Chapter 1 by Trussell provides an overview and guide to the volume and shares thoughts about future research directions. Chapter 2 by Golding examines the voltage-gated ion channels of auditory neurons and how these determine the kind of computation that can be performed on acoustically driven inputs. With this as background, we turn to synapses in Chapter 3, wherein Nicolson shows how the molecular and physiological components of the hair cell synapse initiates coding.

The giant synapses of the auditory system have attracted attention of researchers both within and outside the auditory field, to great advantage. These terminals, the endbulbs and calyces of Held, are described in Chapter 4 by Manis, Xie, Wang, Marrs, and Spirou and also in Chapter 5 by Borst and Rusu. In Chapter 6, MacLeod and Carr describe the bases of synaptic coincidence detection and its role in sound localization, while in Chapter 7, Trussell examines how synaptic inhibition operates, with examples from the cochlear nucleus and superior olive.

Chapter 8 by Metherate and Chapter 9 by Tzounopoulos and Leão address the short- and long-term modifiability of auditory synapses and how this plasticity may be used in auditory processing. Metherate examines auditory neuromodulation and gives an example of its potential roles in attention. Tzounopoulos and Leão present the case for experience-dependent plasticity as a well-established component of auditory function from brainstem to cortex.

As in all previous SHAR volumes, there are chapters in other books of the series that have relevance to the general theme discussed in this volume. For example, the circuitry and computation in the auditory system, so related to synapse function, is discussed in chapters of Volume 15 (*Integrative Functions in the Mammalian*

Auditory Pathway), while synapses in the inner ear are considered in detail in Volume 8 (*The Cochlea*) and Volume 27 (*Vertebrate Hair Cells*). Finally, computational models of the auditory system, the topic of many chapters in this volume, are discussed in detail in Volume 6 (*Auditory Computation*) and Volume 35 (*Computational Models of the Auditory System*).

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Chapter 1
Sound and Synapse

Laurence O. Trussell

1 Introduction

This volume is an expression of the ongoing application of the concepts and techniques of cellular neurophysiology and cell biology to understanding auditory function. Embedded in this application is a story of the fruits of cross fertilization among scientific fields. Rather than apply traditional methods of neuroanatomy, in vivo extracellular recordings, or spike frequency analysis, many labs began asking questions such as what ion channels are expressed in auditory neurons? How do these channels determine the cellular response to sound? Beyond simply identifying which transmitters were expressed in different neurons, scientists explored the biophysical responses to those transmitters and related them to the response times of synapses. Often, these were labs with background and training outside the auditory system. Among the pioneers in this effort were Donata Oertel, who first developed a viable brain slice preparation of the cochlear nucleus and characterized cellular response properties in identified cells (Oertel 1983), and Paul Manis, who first voltage clamped isolated auditory neurons (Manis and Marx 1991). Moreover, some of the most challenging projects in electrophysiology were first applied to the auditory system, such as the application of patch-clamp methods to presynaptic structures like the calyx of Held by Ian Forsythe, Gerard Borst, and colleagues (Forsythe 1994; Borst et al. 1995) or to tiny postsynaptic spiral ganglion cell dendrites by Elisabeth Glowatzki and Paul Fuchs (Glowatzki and Fuchs 2002). This had unexpected benefits: because the language of cellular physiology was common to many neural systems; this effort produced results understandable and of interest to diverse non-auditory neuroscientists and thus helped popularize the field.

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The results of these efforts have triggered a new appreciation of the synapse as a key to understanding auditory mechanisms. Synapses are more than just switches for excitation versus inhibition. Synapses vary in their strength and their ability to sustain activity over time. They vary in their temporal precision, their time course of action, and their ability to change in response to different patterns of activity. A central thesis, even an article of faith, is that this variation occurs in accordance with the particular demands for information processing in a given circuit. What is the physiological advantage conferred by expression of Kv1 K^+ channels in dendrites of coincidence detector cells? Why have a giant calyceal synapse, the largest in the brain, with a low probability for vesicle release? Questions like these motivate one to make teleological sense of "details." As important as these questions are, there is a danger in designing experiments that are yoked to such considerations. Focusing on what "makes sense" to the system presumes a rather complete understanding of the system, and this focus may lead to ignoring information that could eventually be of great consequence. For example, why do synapses in the dorsal cochlear nucleus, the lowest level of the auditory central nervous system (CNS), exhibit such amazingly rich and varied forms of plasticity? Our systems-level understanding of multisensory integration in this region is simply too rudimentary to answer this question. Thus a corollary to the central thesis presented earlier is that unbiased studies of cellular properties may lead to a novel or revised understanding of the system. As a result, it is not always bad practice to consider the circuit as a pretext for doing fascinating, and (dare I say it?) fun, experiments in cellular neuroscience!

2 Overview

The topics in this volume were chosen to highlight areas in which there is abundant insight into cellular function or in which the cellular properties are clearly essential to understanding how a circuit computes. Chapter 2 by Golding provides insight into the intrinsic response properties of neurons, how cells take their synaptic input and turn it into a particular pattern of action potential firing. This is a field that provides an excellent example in which studies of auditory cellular neuroscience must draw constantly from an ever-increasing body of multidisciplinary information. What ion channels are expressed in a given cell? What is their molecular composition and what is the consequence of this structure to their biophysical properties? How are these proteins distributed over the cell surface? How are they regulated and how do they change during development or in disease states? The study of ion channel properties also provides vital information for the construction of computational models that both are valid and have strong predictive power. From this will surely come deep insight into the function of auditory circuits.

Chapter 3 by Nicolson reveals the synaptic genesis of auditory processing in the hair cell. Hair cells transduce mechanical vibration to a voltage change that embodies key temporal and intensity features of sound. The synapse must then convert this voltage change into a neural code in two phases. First, voltage must translate to

vesicle exocytosis in a manner that preserves these aspects of temporal and intensity information. Next, the postsynaptic dendrite must respond to the transmitter, generate an action potential, and then restore itself to be ready to respond again. Recent work has revealed that this is no "garden-variety" synapse; rather, it has the capacity to sustain continued exocytosis and to respond to voltage changes with exquisite temporal precision. Novel proteins are expressed at the synapse, and a remarkable exocytic mechanism called multivesicular release is prominent – presumably these and other novel features somehow figure into the specialized function of the hair cell synapse.

The auditory CNS features some of the largest synapses in the mammalian brain, the endbulbs and calyces of Held, explored in Chap. 4 by Manis, Xie, Wang, Marrs, and Spirou and in Chap. 5 by Borst and Rusu. These giant terminals, each making hundreds of synaptic release sites, have been an attractive preparation for study for a variety of reasons. Because they are so large, endbulbs and calyces are practically begging to be labeled as auditory relays and thus have all their physiological properties interpreted in that context. However, analysis of their detailed properties have revealed many surprises, such as short-term plasticity and presynaptic modulation, giving rise to speculation that such terminals do more than act as relays. Some laboratories approached these terminals with little interest in auditory function, instead taking the opportunity to study an accessible central synapse. Many significant advances have been made in this effort, which have informed a general understanding of how brain synapses work. However, as the results are compared to data in other preparations, it has become clear that endbulbs and calyces are not merely large generic synapses, but also structures highly specialized to specific components of auditory processing.

In Chap. 6, MacLeod and Carr explore how synapses mediate the amazingly precise coincidence detection that mediates some forms of sound localization. Basic components of coincidence detection are the innervation of distinct sets of dendrites, fast-acting transmitter receptors, and ultra-responsive membrane properties. These are features fundamental to function that appear be common to all vertebrates. Some aspects of sound localization, however, differ between birds and mammals, and perhaps even among some mammals. These may have resulted from animals' different frequency ranges of hearing and different head sizes, which determine what physical properties of sound are relevant and limit how circuits can extract information. For example, synaptic inhibition has been employed in different ways by mammals and birds, a topic of intense current debate. Although it is believed that inhibition is needed for refining coincidence detection, in fact inhibitory transmission of diverse types appears at every level of auditory processing and must therefore serve many functions. In Chap. 7, Trussell overviews mechanisms of synaptic inhibition and gives examples from two very different inhibitory pathways in the cochlear nucleus and superior olive. However, although there are some well-known examples of inhibition in the auditory system, the field is very young in terms of defining what are the variety of inhibitory cells, how each cell type modifies excitation at its different target cells, and how experience-dependent plasticity, drugs, or disease affects hearing through alterations in inhibition. Moreover, it is

likely that in the world of intelligent design of prosthetic devices, construction of brainstem implants that mediate hearing in patients with damaged auditory nerves will have to account for refinements in processing imposed by inhibitory neurons.

A common misconception about auditory processing, especially in the lower auditory pathways, is that it needs to be invariant, to respond the same way at all times. Otherwise, preservation of fine temporal differences in the information contained in sound signals might be disturbed, thus compromising perception. Chapter 8 by Metherate and Chap. 9 by Tzounopoulos and Leão show that this view is not valid. Metherate defines for us the rather slippery term "neuromodulation" and discusses how it makes sense as a vital function for an auditory system that must operate in different situations with different states of attention. Tzounopoulos and Leão explore in detail how experience-dependent plasticity is a well-established part of auditory function, in the cortex, where it might be expected, but also in the lowest levels of auditory processing.

3 New Horizons

This introduction has tried to convey that our understanding of synaptic mechanisms in audition has required bringing in new skills sets and new outlooks. What new areas of research must come into the field to deepen our understanding of auditory function? Many of the chapters herein conclude with a look to the future. To the many insightful points they have made can be added the need to look at the functional significance of the complex array of descending connections within the auditory system. Being able to label vitally, and preferably to activate single axons, perhaps optogenetically, in identified descending pathways will bring clarity to a major area of research. Testing the role of single cells or single synapses by acute inactivate with modern genetic and molecular biological tools will be essential. Network-level computational models must take into account the kinds of work outlined in this volume.

Finally, it may be noted that many of the chapters in this book address exclusively synaptic mechanisms in auditory brainstem. Although there is much excellent work in cortex, by and large the studies of synaptic function are in their infancy for levels higher than the superior olive, including the lemniscal nuclei, the inferior colliculus, and the thalamus. One reason for this is the great complexity of their inputs. Even when recordings are made from identified cell types, it is difficult to identify the source of a particular excitatory or inhibitory input, especially when studied in vitro. New approaches to recording and stimulation, as well as new preparations, must be developed to extend the work outlined here through the full extent of the auditory system.

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References

Borst, J. G., Helmchen, F., & Sakmann, B. (1995). Pre- and postsynaptic whole-cell recordings in the medial nucleus of the trapezoid body of the rat. *Journal of Physiology, 489 (Pt 3)*, 825–840.

Forsythe, I. D. (1994). Direct patch recording from identified presynaptic terminals mediating glutamatergic EPSCs in the rat CNS, in vitro. *Journal of Physiology, 479 (Pt 3)*, 381–387.

Glowatzki, E., & Fuchs, P. A. (2002). Transmitter release at the hair cell ribbon synapse. *Nature Neuroscience, 5*(2), 147–154. doi: 10.1038/nn796.

Manis, P. B., & Marx, S. O. (1991). Outward currents in isolated ventral cochlear nucleus neurons. *Journal of Neuroscience, 11*(9), 2865–2880.

Oertel, D. (1983). Synaptic responses and electrical properties of cells in brain slices of the mouse anteroventral cochlear nucleus. *Journal of Neuroscience, 3*(10), 2043–2053.

Chapter 2
Neuronal Response Properties and Voltage-Gated Ion Channels in the Auditory System

Nace L. Golding

1 Introduction

One of the central challenges to auditory neuroscience is to understand how sound information is processed and transformed as it ascends to different levels in the brain. One way that the central auditory system is distinct from other sensory areas of the brain is the extent to which sound information is segregated at the earliest subcortical areas into different ascending pathways encoding different aspects of sound. For example, in the visual system, the first stage of information processing in the brain takes place in the lateral geniculate nucleus of the thalamus before proceeding directly to the primary visual cortex, where many of the major transformations in visual receptive fields occur. In olfaction, although extensive processing occurs in the olfactory bulb prior to the cortex, it is not apparent that there are topographic differences in how olfactory information is processed.

The aim of this chapter is to review how the coding of auditory information in different ascending pathways is influenced by synaptic integration, the process by which excitatory and inhibitory inputs sum together and trigger patterns of action potentials that reflect salient features of sounds. It will be made clear in this chapter that synaptic integration is strongly influenced, and in some cases dominated, by interactions between synaptic inputs and different classes of voltage-gated ion channels. Although mammalian systems are the primary focus, work from the avian auditory system will be discussed in specific instances. Particular attention will be on neurons of the cochlear nucleus and superior olivary complex, where the role of

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voltage-gated ion channels can be more easily understood within the context of well-defined circuit computations and functional roles. Two broad classes of neurons emerge: those with electrical properties that precisely maintain the temporal features encoded in their auditory inputs and those with electrical properties that transform synaptic input patterns into new patterns.

2 The Spatial and Temporal Structure of Auditory Input to the Brain

In order to understand the nature of different auditory neurons' responses to sound stimuli, it is important to review two fundamental concepts in auditory neuroscience: tonotopy and phase locking. Sounds of different frequencies vibrate the basilar membrane of the cochlea in a topographic manner, with low frequencies vibrating more apical locations and high frequencies vibrating more basal locations. These vibrations are transduced into graded electrical signals by the cochlear hair cells, which in turn trigger patterns of action potentials in the spiral ganglion neurons (Nicolson, Chap. 3). Because neurons in the spiral ganglion innervate a limited number of hair cells, each ganglion cell carries information about a limited range of frequencies. Deflections of the stereocilia embedded in the basilar membrane cause a depolarization that leads to activation of voltage-gated calcium channels, causing calcium influx and the release of the excitatory neurotransmitter glutamate onto the endings of the spiral ganglion neurons. The activity of hair cells is converted into trains of action potentials by the spiral ganglion cells whose axons project to the brain via the eighth cranial, or auditory, nerve. All auditory information to the brain is carried by the auditory nerve fibers, which in turn synapse onto diverse cell targets in the cochlear nucleus, the first and obligatory integrative station in the brain. The cochlear nucleus possesses at least six classes of projecting neurons. Each of these pathways conveys different kinds of information, despite the fact that the presynaptic pattern of action potentials to these neurons is the same. There is an orderly representation of frequencies imposed by the paths of these auditory afferents in the brain. Their parallel orientation to one another in the cochlear nucleus creates a series of "iso-frequency" slabs, imposing frequency selectivity on the different cell types present in the cochlear nucleus. This organization is maintained through the projection patterns of neurons in the cochlear nucleus, thus creating tonotopic maps at successively higher levels in the auditory pathway.

Auditory afferents also convey critical information about sounds due to their ability to precisely represent periodic information in the patterns of their action potential output. This is commonly referred to as temporal coding. In hair cells, timed neurotransmitter release is brought about by the fact that hair cell signaling is directionally selective, with positive deflections of the stereocilia (toward the tallest stereocilia) triggering membrane depolarization and negative deflections resulting in membrane hyperpolarization. Thus, during acoustic deflections of the basilar membrane, hair

cells respond with cyclical depolarizing and hyperpolarizing voltage changes that reflect the frequency content of the stimulus. The corresponding cyclical release of neurotransmitter onto spiral ganglion cells imposes a restricted interval over which firing occurs, a phenomenon known as phase locking. In auditory nerve fibers, the axons of spiral ganglion neurons, phase locking occurs at frequencies generally below 2–4 kHz in mammals but extends up to 9 kHz in barn owls (Johnson 1980; Köppl 1997; Taberner and Liberman 2005). It is important to note that the precise phase locking of an individual auditory neuron does not require perfect one-for-one firing with each cycle of the acoustic stimulus. As many neurons encode a given frequency, the interval of the stimulus is encoded by the overall firing responses of the neural population as a whole.

3 Synaptic and Voltage-Gated Ion Channel Properties for Precise Temporal Coding

Given the importance of timing information in the auditory system, a major focus of this chapter is on how interactions between synaptic inputs and voltage-gated ion channels maintain, and in some cases improve, the precision of the firing of action potentials. Some of the most intensely studied circuits that utilize timing information are introduced here.

3.1 Circuits That Utilize Timing Information

3.1.1 Coincidence Detection Across Frequencies in Octopus Cells of the Ventral Cochlear Nucleus

Octopus cells are located in a distinct area of the posteroventral cochlear nucleus called the octopus cell area (Osen 1969). Their axons form a major ascending projection, giving rise to large calyceal endings in the contralateral ventral nucleus of the lateral lemniscus as well as the superior paraolivary nuclei (reviewed in Oertel 1999). These neurons are named after their distinctive dendritic architecture, which consists of large-caliber dendrites emanating from one pole of the soma. Octopus cells exhibit a distinct orientation with respect to the paths of the auditory nerve fibers, which provide their primary excitation. The cell body tends to be oriented toward the posterior octopus cell area, which receives inputs from lower-frequency afferents, and the dendrites extend roughly perpendicularly to the paths of the auditory nerve fibers toward higher-frequency regions (Fig. 2.1a) (Osen 1969; Kane 1973). Accordingly, octopus cells in vivo exhibit broad tuning curves and are effectively driven by transient broadband stimuli such as clicks (Godfrey et al. 1975;

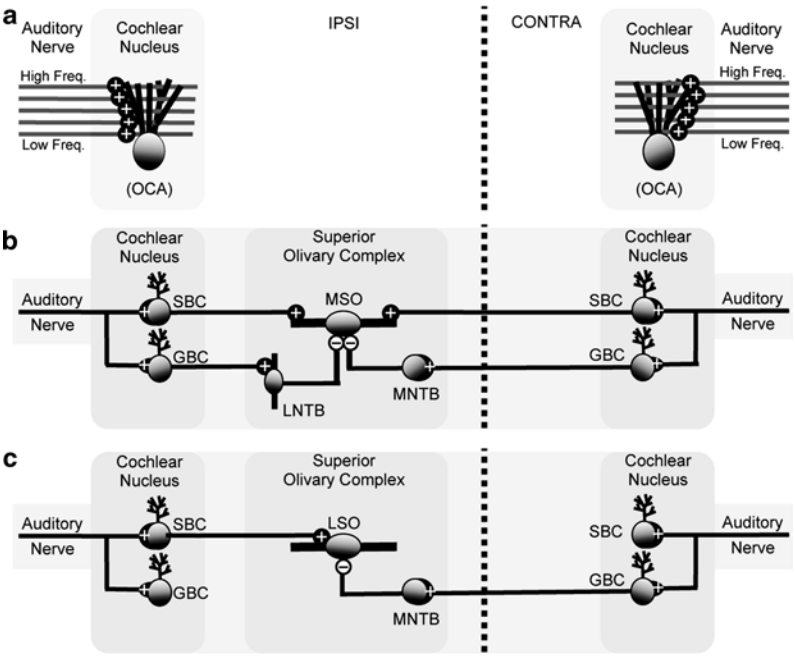

Fig. 2.1 Three time-coding pathways in the auditory brainstem. (**a**) Octopus cells are clustered in a distinctive area of the posteroventral cochlear nucleus, the octopus cell area (OCA). Excitatory, glutamatergic inputs from auditory nerve fibers are organized tonotopically, with low-frequency fibers forming synapses on more proximal dendrites and higher-frequency fibers contacting progressively more distal dendrites. (**b**) Excitatory synaptic coincidence detection of binaural inputs in the medial superior olive (MSO). MSO principal neurons present in the superior olivary complex receive glutamatergic excitation from both ipsilateral and contralateral spherical bushy cells (SBCs) in the anteroventral cochlear nucleus, which in turn are driven by large calyceal synapses of auditory nerve fibers, the endbulbs of Held. MSO neurons are driven by two feedforward inhibitory nuclei, the medial and lateral nuclei of the trapezoid body (MNTB and LNTB). Both neuron types are primarily glycinergic and are driven by excitation from globular bushy cells (GBCs) of the posteroventral cochlear nucleus. Glycinergic inhibition in MSO principal neurons is targeted to the soma and proximal dendrites, whereas excitation is primarily dendritic and segregated to one side of a bipolar arbor. (**c**) Binaural processing in the lateral superior olive (LSO). LSO principal neurons receive ipsilateral excitation from ipsilateral spherical bushy cells and contralateral inhibition from MNTB principal cells. Similar to MSO principal neurons, LSO principal neurons receive somatic/proximal dendritic inhibition and dendritic excitation within a bipolar dendritic structure

Rhode and Smith 1986; Oertel et al. 2000). In response to tones and noise stimuli, octopus cells respond with an "onset" firing pattern, with a single well-timed spike followed by nearly no subsequent firing for the duration of the sound stimulus. Octopus cells likely integrate the convergence of at least 50 auditory nerve fibers (Golding et al. 1995). Because each input contributes only a small submillivolt depolarization to octopus cells' postsynaptic responses, the initiation of action potentials requires strong synchronous activation of many auditory nerve fibers

tuned to a broad range of frequencies. In this way, octopus cell dendrites detect the coincident activity of a large population of auditory nerve fibers encoding a broad range of frequencies.

3.1.2 Computation of Interaural Time Differences in the Medial Superior Olive

Neurons of the medial superior olive (MSO) are one of the major cell groups in the superior olivary complex and will be described, along with their avian homologs, in Chap. 6 by McLeod and Carr. The MSO is one of the first sites for integrating auditory activity from the two ears. MSO neurons are innervated by the spherical bushy cells that reside in the ipsilateral and contralateral ventral cochlear nucleus (Fig. 2.1b) (Cant and Casseday 1986; Smith et al. 1993; Beckius et al. 1999). Spherical bushy cells themselves are driven by only a few (1–3) powerful specialized endings from the auditory nerve, the endbulbs of Held (Manis et al., Chap. 4). The spherical bushy cells then provide conventional bouton-type excitatory synapses to MSO principal cells. The dendritic architecture of MSO principal cells is bipolar, with ipsilateral bushy cell input segregated to the lateral dendrites and contralateral bushy cells inputs restricted to the medial dendrites (Stotler 1953; Lindsey 1975). MSO neuron responses are also shaped by two feed-forward inhibitory nuclei, the medial and lateral nucleus of the trapezoid body (MNTB and LNTB, respectively). The principal neurons of the MNTB and LNTB are driven by contralateral and ipsilateral globular bushy cells in the cochlear nucleus, respectively (Borst and Rusu, Chap. 5).

As low-frequency sound sources move along the horizontal plane, the relative timing of bushy cell inputs to the superior olivary complex changes systematically, thereby changing the relative timing of excitatory and inhibitory inputs to MSO neurons. MSO neurons respond to these synaptic alterations by changing their rate of action potential firing. This activity is conveyed via the axonal projections of MSO neurons to the central nucleus of the inferior colliculus (Henkel and Spangler 1983; Nordeen et al. 1983; Loftus et al. 2004). In this way, MSO neurons detect the relative coincidence of synaptic inputs driven by the two ears and translate these differences into a rate code. Ultimately, this activity is utilized for the localization of sounds along the horizontal plane. Thus, the temporal resolution of the detection of binaural coincidence in the MSO has a clear relationship to the spatial acuity of horizontal sound localization.

3.1.3 Computation of Interaural Level Difference in the Lateral Superior Olive

Neurons in the lateral superior olive (LSO) comprise the second major integrative stage for processing binaural cues in the auditory brainstem. The principal neurons of the LSO vary their rate of action potential firing according to differences in the level of sound intensity between the two ears. These level differences are most acute