SYNAPTIC MECHANISMS IN AUDITORY CORTEX FUNCTION

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1. ABSTRACT

Neurons in the auditory cortex (AC) respond to acoustic stimuli in diverse ways. Short latency responses code for the physical properties of stimuli, i.e., their frequency and intensity, whereas longer latency potentials may code for behavioral significance or other features. Despite a huge number of studies that, over the years, have reported on acoustic-evoked short and long-latency potentials, remarkably little is understood regarding the cellular mechanisms underlying these responses. Such information is critical to a full understanding of auditory information processing. This review summarizes the available data on synaptic and cellular mechanisms in AC neurons that have been obtained using electrophysiological methods with *in vivo* and *in vitro* preparations. It is apparent that the fundamental mechanisms identified in recent studies can be used in the near future to develop an integrated understanding of the cellular bases of information processing in auditory cortex.

2. INTRODUCTION

In literally thousands of studies over several decades, scientists have measured the electrophysiological responses of AC to acoustic stimulation. Studies include those attempting to determine cortical representations of the acoustic environment (1, 2, 3, 4), animal behavioral studies involving acoustic cues (5, 6), and human psychophysical experiments (1, 7, 8). Acoustic stimuli can elicit a variety of potentials within AC (see below), including short-latency, highly-consistent responses that code for the physical properties of the acoustic stimulus (e.g., its frequency and intensity), as well as longer-latency, labile responses that vary with behavioral state and context (e.g., event-related potentials). Given the diverse research endeavors that utilize auditory evoked responses, it is remarkable how poorly we understand the underlying mechanisms. Determining the cellular bases of evoked responses represents an important

step towards understanding how AC processes acoustic information.

In this review, I will summarize the state of knowledge regarding cellular contributions to AC function. Electrophysiological approaches reveal functional mechanisms most directly, and I will review primarily those studies of AC that have utilized intracellular recording techniques. Two broad methodological approaches involve the use of *in vivo* and *in vitro* preparations. These complementary approaches have been quite useful, since *in vivo* preparations allow for sensory stimulation but are notoriously difficult preparations from which to obtain intracellular recordings, whereas brain slices assist the dissection of cellular mechanisms involving local, but not long-distance, circuitry. The goal of this review is to synthesize what is known and identify what is yet to be determined in order to understand mechanisms of information processing in AC.

3. WHY STUDY SYNAPTIC MECHANISMS IN AUDITORY CORTEX?

The output of a neuron is all-or-none -- the action potential. The vast majority of higher nervous system function occurs "below the surface", at the subthreshold level. The integration of afferent inputs from different sources and the modulation of neuronal activity during diverse brain or behavioral states can not be examined directly in extracellular studies. Thus, to understand these and related functions, one must observe mechanisms at the synaptic and cellular level. Studies of synaptic physiology reveal mechanisms underlying brain function, in "real time". We observe how the brain works, as it works. As with other sensory systems, we approach the study of AC assuming that its function is to process acoustic stimuli, and that by studying this we are

observing the cortex doing what it is meant to do. This may hold true only to a limited extent, but it serves as a reasonable and useful starting position.

Thus, intracellular studies of synaptic mechanisms are a direct window into the workings of AC. At a minimum, they reveal can subthreshold events that lead to cell output, e.g., how sensory-evoked excitatory and inhibitory postsynaptic potentials (EPSPs and IPSPs) sum to produce, or suppress, action potential discharge. Similarly, they can identify aspects of sensory integration that occur at the cortical level (e.g., reduction of excitation due to cortical inhibition) as compared to those characteristics that result from interactions at lower auditory centers that are simply relayed to the cortex. Thus, at a minimum, intracellular studies can reveal cortical contributions to the processing of acoustic signals. However, intracellular studies can reveal much more -- how complex mechanisms such as voltage-dependent processes or neurotransmitter receptor subtypes contribute to integrative functions. It is to answer such questions that intracellular recordings are used most powerfully.

4. WHAT DETERMINES A NEURON S BEHAVIOR ?

Several factors determine when, and how, neurons discharge in response to acoustic stimuli. Chief among these are the types of synaptic inputs elicited. Glutamate-mediated EPSPs and gamma-aminobutyric acid (GABA) -mediated IPSPs are the fastest means to excite or inhibit, respectively, cortical neurons. Integration of EPSPs and IPSPs determine if neurons do, or do not, discharge, and temporal and spatial summation of inputs play an important role. Thus, bursts of excitatory inputs are more likely to excite cortical neurons than an equal number of inputs discharging at longer intervals, due to the effects of nonlinear summation. Conversely, IPSPs can inhibit primarily by two mechanisms, hyperpolarizing and shunting. Hyperpolarization drives the neuron further from spike threshold, whereas shunting inhibition results from decreased membrane resistance due to a greater number of open (usually Cl-) channels. The decreased resistance reduces the efficacy of, or "shunts", afferent EPSPs. Shunting inhibition may be particularly important for cortex, since it appears that IPSP reversal potentials are positive to the resting potential in many cortical neurons (9, 10). Thus, if activation of inhibitory synapses results in a depolarizing potential, or even no overt potential (i.e., the membrane potential is at the IPSP reversal level), the effect can be one of inhibition due to shunting. That being said, while there is clear evidence for hyperpolarizing inhibition in sensory cortex, evidence for shunting inhibition has been more difficult to obtain (11, 12, 13).

Much attention has been paid to GABAergic interneurons given their profound influence over cortical excitability. These neurons are found in all cortical layers (14) and often synapse preferentially with the somas, proximal dendrites, and axon initial segments of the far more common pyramidal neurons (15, 16). There they exert overwhelming control over neuronal discharge, since spike generation occurs most readily at the axon initial segment (17,

18). In sensory cortex, local blockade of GABA-A receptors has demonstrated their critical importance in determining receptive field properties (19, 20, 21). More widespread blockade of GABA-A receptors leads to global seizure activity (22). The presence of an IPSP in sensory-evoked responses is taken to reflect processes occurring at the cortex, since thalamocortical projection neurons are thought to be exclusively excitatory (14, 23, 24). However, extrathalamic projections to cortex may be GABAergic, such as inputs from the basal forebrain and zona inserta (25, 26). It is not known if these inputs contribute to evoked cortical responses.

4.1 Slow synaptic potentials and neuromodulation

Slow synaptic potentials differ qualitatively from fast potentials, and can radically alter a neuron's response to afferent input. Most slow potentials differ mechanistically as well, since they depend on intracellular biochemical, or "metabotropic", processes, unlike fast "ionotropic" synaptic transmission that utilizes ion channels contained within the neurotransmitter receptor complex. Metabotropic activity underlies neuromodulation, the alteration of neuron's excitability by intracellular processes activated by synaptic stimulation. For example, several types of K+ channel are regulated by neurotransmitters acting via intracellular (G-protein mediated) mechanisms (27). Synaptic stimulation often reduces K+ permeability (e.g., due to stimulation of adrenergic beta receptors, or muscarinic M1 receptors), although increased K+ permeability also can occur (e.g., stimulation of muscarinic M2 receptors). The closure of K+ channels will increase membrane excitability (the opposite effect to shunting inhibition) and increase length and timeconstants to enhance the integration of inputs to different parts of the neuron. Depending on the intracellular mechanism involved, such effects can last for minutes or even hours (28). Since a neuron at rest exhibits K+ efflux (the K+ leak current), closure of these channels will lead to a depolarization -- a slow, "conductance decrease" EPSP. Thus, slow synaptic potentials produced by release of acetylcholine, norepinephrine or other transmitters with neuromodulatory actions can alter neuronal excitability for long periods of time.

Neuromodulation by the diffuse neurotransmitter systems that originate primarily in the brainstem (the original ascending reticular activating system, ARAS (29)) likely underlies changes in information processing during different brain states (e.g., sleep vs. waking). The mechanisms of these changes are complex, reflecting modulation of individual neurons resulting in altered "emergent" properties of thalamocortical and cortical networks (30). The role of neuromodulation in higher order functions (e.g., attention) is considerably less obvious, as is the relationship of slow synaptic potentials to long-latency, long-duration extracellular potentials (5, 31, 32, 33). Future research must address these issues further.

4.2 Intrinsic membrane properties

Cortical neurons respond to inputs in diverse ways, depending on the types and distribution of ion channels found in their membranes. Intrinsic membrane properties are inferred from neuronal responses to intracellular current pulses, are used to classify neurons electrophysiologically,
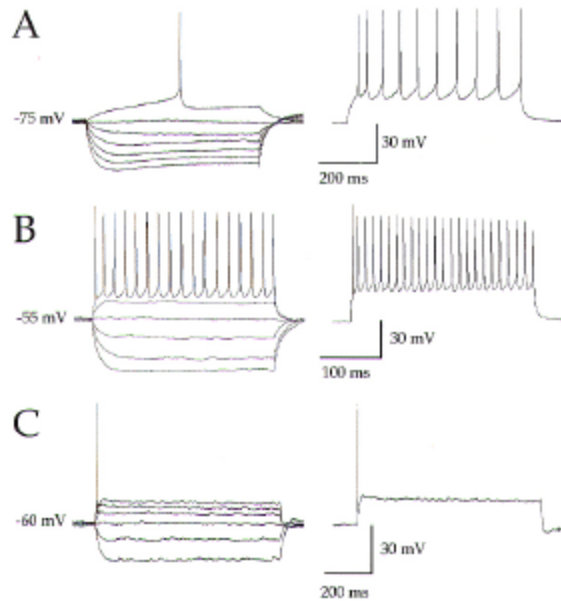
Figure 1. Examples of intrinsic membrane properties for three types of neuron in auditory cortex. All data were obtained using whole-cell (patch pipette) recordings from neurons visualized in AC brain slices. A. Traces show Regular-Spiking electrophysiology that is characteristic of some pyramidal neurons. Rectangular current pulses (not shown) were delivered *via* the recording electrode. The current pulses produced hyperpolarizing voltage responses and one depolarizing response to spike threshold (traces on left, -0.1 nA to +0.2 nA in 0.02 nA steps). Single response on the right is to +0.6 nA. Adaptation of discharge to a maintained stimulus is characteristic of Regular Spiking neurons. B. Typical Fast-Spiking physiology that is characteristic of one type of GABAergic interneuron. Neuron discharges at high rate with no adaptation. Subthreshold responses are to -0.3 to +0.1 nA current pulses in 0.1 nA steps; suprathreshold responses are to 0.3 and 0.5 nA pulses. C. This cell discharged only one spike to suprathreshold current pulses, and showed evidence of rectification in the depolarizing direction. Current pulses were -0.2 to +0.4 nA in 0.1 nA steps.

and undoubtedly contribute to functional characteristics. In a now classic study (10), cortical neurons were grouped into "regular spiking", "intrinsic bursting" and "fast spiking" neurons based on their spiking pattern in response to depolarizing current pulses (figure 1). Morphological identification indicated that regular spiking and intrinsic bursting neurons were pyramidal neurons, whereas fast spiking cells were GABAergic interneurons. Subsequent studies have modified and expanded the original classification scheme. For example, there appear to be subtypes of regular spiking cells (34), and not all GABAergic interneurons are fast spiking (in fact, some are regular spiking) (35, 36, 37). However, it is clear that cortical neurons have diverse intrinsic properties, and these likely allow for different functional contributions to cortical circuits. The interactions of synaptic inputs with intrinsic properties may give rise to unpredictable emergent properties of cortical networks.

5. RESPONSES OF AUDITORY CORTEX TO ACOUSTIC STIMULI.

To appreciate cellular mechanisms in AC, it is helpful to review briefly the kinds of stimuli to which AC neurons respond. Well-established features of primary AC include the orderly representation of stimulus frequency, or tonotopic arrangement (and the resulting formation of isofrequency bands), and the sensitivity of neurons to binaural stimuli (1, 2, 3, 4, 38). These features reflect the ability of AC neurons to code for physical properties of acoustic stimuli including their frequency, intensity, and location in space. Neurons in primary AC respond with lowest threshold to a single frequency, the characteristic frequency (CF), and respond with higher thresholds to other, nearby frequencies. At CF, neurons respond to steadily increasing stimulus intensities either with firing rates that increase to a point and then plateau (producing monotonic intensity functions) or rates that increase to a point and then decrease (nonmonotonic functions). Sound waves from acoustic sources in the environment take different paths to each ear, and produce interaural time and intensity differences (ITDs and IIDs) at the two ears. These differences are used by neurons in several auditory regions to code for stimulus location. In AC, neurons optimally code ITDs and IIDs that reflect stimuli within 45 deg of the position directly in front of the animal (1). The involvement of AC in processing information about frequency and location has been implied by lesion studies. For example, lesioning an entire isofrequency band impairs the ability of animals to determine the location of a sound of that frequency (6). Conversely, lesions that encompassed all of AC except for a narrow isofrequency band leaves animals unable to discriminate the location of sounds *except* for the frequency of the spared representation.

Auditory event-related potentials (ERPs) are extracellular field potentials elicited in response to acoustic events. Because they can involve noninvasive recording techniques, ERPs are used extensively in studies of animal behavior and human psychophysics (7). Some ERP components are modified by psychological processes such as attention, whereas other components may reflect pre-attentive automatic feature analysis (e.g., the mismatch negativity, MMN). Only the earliest ERP components ($\leq$ 20 ms latency) overlap with the single unit responses of auditory physiology studies, and very little is understood regarding the mechanisms underlying longer-latency components (with latencies up to several hundred ms). Long-latency potentials may involve diffuse neuromodulatory systems (32, 39) or slow ionotropic mechanisms (40, 41).

6. SYNAPTIC MECHANISMS IN AUDITORY CORTEX *IN VIVO*

As described above, there is a wealth of information to be gained by direct observation of synaptic integration during the processing of auditory stimuli. Unfortunately, there have been remarkably few attempts to do so, no doubt due to the difficulty of obtaining stable intracellular recordings in intact animals. The earliest attempts compared subthreshold (synaptic potentials) and suprathreshold (spikes) responses in unanesthetized, paralyzed cats (42, 43), and the findings were confirmed more
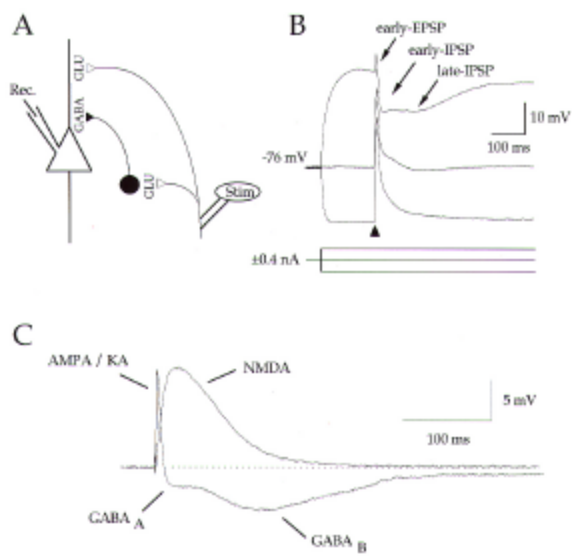
Figure 2. Excitatory and inhibitory synaptic potentials from AC neurons *in vitro*. A. Schematic shows a hypothetical local circuit. Whole-cell recording from layer III pyramidal neuron, stimulation of layer VI region within the same cortical column. B. Single stimulus pulse elicits an early-EPSP followed by early and late IPSPs. Stimulation during membrane depolarization and hyperpolarization demonstrates different reversal potentials for the three synaptic responses. C. Pharmacological manipulations indicate that the three synaptic potentials are mediated by AMPA/KA, GABA-A, and GABA-B receptors, respectively. A fourth potential, the NMDA receptor-mediated late-EPSP, is suppressed by inhibitory potentials, and may only appear as a "hump" between the two IPSPs. In C, the full late-EPSP (superimposed on the control traces) was observed after pharmacological reduction of IPSPs.

recently with extracellular and intracellular recordings in ketamine-anesthetized cats (44, 45). These studies verified that response properties (defined by spike discharge in response to pure tones, noise bursts, clicks, or click trains), determined during intracellular recordings were similar to those determined extracellularly. That is, impalement with the microelectrode did not alter the response properties of the cell. As expected, acoustic-evoked EPSPs gave rise to spike discharge and evoked IPSPs suppressed spikes. IPSPs hyperpolarized neurons and produced a large reduction in input resistance (45). Most neurons that did not discharge in response to stimuli nevertheless displayed subthreshold synaptic potentials, indicating that more neurons receive auditory inputs than respond with action potentials, even in unanesthetized preparations. Similarly, the range of stimulus frequencies and intensities that elicited spikes was narrower that the range that elicited synaptic responses. At times, complex interactions of evoked EPSPs and IPSPs shaped response properties, for example producing onset excitation followed by inhibition in some cells, and sustained excitation or inhibition in other cases.

Other intracellular studies of AC have not utilized sensory stimulation, but have characterized the subthreshold responses elicited by stimulation of regions that project to AC

(46, 47), as well as the types of neurons found in AC and their processes (48, 49, 50). The interaction of one neuromodulatory system, the basal forebrain cholinergic system, with AC has been determined in intracellular and extracellular studies (47, 51, 52, 53). Stimulation of cholinergic afferents generally enhanced synaptic responses elicited by stimulation of the auditory thalamus (but see (53)). However, cholinergic neuromodulation of frequency receptive fields may be more complex (54, 55, 56, 57, 58).

7. SYNAPTIC MECHANISMS IN AUDITORY CORTEX *IN VITRO*

As with all brain slice preparations, the AC slice has the advantage of enabling precise intracellular and pharmacological manipulations in a preparation with intact local circuitry. The disadvantage, of course, is that the slice does not preserve long distance connections. Several studies have used brain slices to determine the intrinsic membrane properties, synaptic mechanisms, and neuromodulation of AC neurons. To a large extent, the intrinsic and synaptic characteristics of AC neurons are shared with cortical neurons in general (10, 59, 60, 61, 62), but there are potentially important differences.

Electrical stimulation within the same cortical "column" as a recorded pyramidal neuron produces a overlapping series of two EPSPs and two IPSPs (figure 2) (63, 64). The responses are characterized by differential sensitivity to pharmacological agents, different latencies and time courses, and different reversal potentials. The neurotransmitters glutamate and GABA are responsible for the excitatory and inhibitory potentials, respectively, each one acting at two receptor subtypes. The potentials are, in order of latency, i) an early-EPSP produced by glutamate acting at alpha-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid/kainate (AMPA/KA) receptors, ii) an early-IPSP mediated by GABA-A receptors, iii) a late-EPSP mediated by *N*-methyl-D-aspartate (NMDA) -type glutamate receptors, and iv) a late-IPSP mediated by GABA-B receptors. The potentials overlap greatly, making individual characterizations difficult without further manipulations and emphasizing the potential for complex interactions. The early-EPSP has conventional EPSP voltage-dependence, becoming smaller with membrane depolarization and larger with hyperpolarization, whereas the late-EPSP has nonconventional (opposite) voltage-dependence due to the involvement of the NMDA receptor (65). Since the GABA-A receptor is coupled to a Cl- channel and the GABA-B receptor opens a K+ channel, the early-IPSP has a reversal potential (~-70 mV) near the resting potential, whereas the late-IPSP has a more negative reversal potential (~-90 mV). Thus, the four potentials can be separated by their voltage-dependence as well as other criteria.

The four synaptic responses are differentially activated by stimulation of different intensities and modified by patterned stimulation (12, 60, 61, 62, 64). Threshold stimulus intensities elicit the early-EPSP alone whereas slightly higher intensities activate both early and late-EPSPs. Still higher intensities recruit the early and late IPSPs. Activation of the IPSPs strongly suppresses the late-EPSP and

cuts short the early-EPSP, however, this suppression can be lifted by repetitive stimulation which rapidly fatigues IPSPs (66). Repetitive stimulation also fatigues the late-EPSP rapidly, with a lesser effect on the early-EPSP. It is clear that these four potentials can lead to a variety of response configurations with unknown consequences for information processing in AC. It may be important to point out that disinhibition of the NMDA receptor-mediated late-EPSP by fatigue of IPSPs may lead to profound changes in cellular function. In fact, repetitive stimulation of afferents can produce long-term potentiation of synaptic potentials in AC (67).

The response of AC neurons to selective activation of afferents from the auditory thalamus may be different than their response to activation of intracortical afferents. Recently, an *in vitro* preparation has been developed that maintains the auditory thalamocortical pathway intact (68). Stimulation of thalamocortical afferents elicits in AC neurons an early-EPSP followed by a slow depolarization with superimposed intermixed rapid EPSPs and IPSPs. This activity endures for up to several hundred ms. It is hypothesized that the rapid fluctuations reflect the activation of neuronal ensembles within AC. The contribution of such activity to the processing of acoustic information in the intact animal remains to be determined.

Neuromodulation of AC neurons also has been studied *in vitro*. Stimulation of cholinergic afferents produces a slow depolarization with a duration of seconds, and increased membrane resistance in AC pyramidal neurons (51, 69). Cholinergic inputs also increase membrane oscillations in some AC neurons, and modify the intrinsic properties of bursting neurons in layer V so that they respond to maintained depolarization with single spikes rather than burst firing. These effects are hypothesized to contribute to the changes in information processing that occur in the cortex upon arousal (30, 33). Such changes include enhanced responses to excitatory glutamatergic inputs (52, 70).

For the most part, the intrinsic membrane properties of AC neurons resemble those reported for other cortical areas (figure 1). A potentially important exception is depicted in figure 1C. For such cells, depolarizing current pulses of different magnitudes elicit only 1 or a few spikes initially, before the discharge stops abruptly. These neurons show striking rectification in the depolarizing direction, as indicated by overlapping voltage responses to steadily increasing current pulses. Such intrinsic electrophysiology has gone largely unreported in studies of neurons from other cortical regions (10, 35, 37), but was exhibited by ~20% of cells in a recent study of layer IV neurons in AC (R. Metherate, unpublished data). Interestingly, neurons with similar discharge patterns and striking outward rectification occur in lower auditory nuclei (71), suggesting that such intrinsic physiology is functionally important at several levels of the auditory pathway. The ability of auditory neurons to code brief transients, or intervals between nearly-coincident inputs, may depend on similar cellular mechanisms (72).

8. PERSPECTIVE

It should be clear from this brief review that a considerable amount of information is known regarding the synaptic and cellular electrophysiology of auditory cortex. Equally clear is that there are obvious questions to be answered in future experiments. The short latency excitation and inhibition of AC neurons is due to the activation of fast EPSPs and IPSPs, most likely mediated by AMPA/KA and GABA-A receptors, respectively. However, it is not clear how slower EPSPs and IPSPs mediated by NMDA and GABA-B receptors, respectively, contribute to acoustic responses. These synaptic potentials are easily elicited in vitro, but their role in sensory processing in vivo remains unknown. Similarly, while reduction of spike activity has been associated with IPSPs in several instances, much work needs to be done to understand the range of functions performed by cortical inhibitory activity. Since sensory-evoked inhibitory activity is thought to originate primarily within the cortex, answering these questions also will provide information about cortical contributions to the processing of acoustic information. For example, the reduction of firing rates at high stimulus intensities for neurons with nonmonotonic intensity functions could result either from the recruitment of cortical inhibitory interneurons, and therefore be evident as enhanced IPSPs, or from reduction of afferent excitation due to activity in lower auditory pathways. The latter mechanism would result in smaller-amplitude evoked EPSPs in the cortex, with no evidence for IPSPs. Similar issues can be addressed regarding responses to binaural inputs.

The influence of neuromodulatory activity on acoustic-evoked synaptic potentials also should be determined. That brain arousal systems modify sensory processing is unquestioned, but the mechanisms involved are not clear. Recent demonstrations that the basal forebrain cholinergic system may dramatically regulate the response properties of AC neurons (56, 57, 58, 73) reinforces the need for systematic cellular studies.

Finally, several studies have classified AC and other neurons based on intrinsic electrophysiology and morphology. It remains to be determine how intrinsic properties shape responses to acoustic stimuli. Since intrinsic membrane properties determine the pattern and number of spikes elicited by excitatory inputs, they may combine with synaptic potentials to determine unique response properties of AC neurons.

Using electrophysiological and anatomical approaches in vivo and in vitro, a great deal of information has been acquired regarding the auditory physiology of AC neurons on the one hand, and cellular and synaptic physiology of AC neurons on the other. By combining these approaches, we draw closer to the goal of understanding the cellular bases of information processing in the auditory cortex.

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