Inhibitory Neural Circuits in the Mammalian Auditory Midbrain

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ABSTRACT: The auditory midbrain is the critical integration center in the auditory pathway of vertebrates. Synaptic inhibition plays a key role during information processing in the auditory midbrain, and these inhibitory neural circuits are seen in all vertebrates and are likely essential for hearing. Here, we review the structure and function of the inhibitory neural circuits of the auditory midbrain. First, we provide an overview on how these inhibitory circuits are organized within different clades of vertebrates. Next, we focus on recent findings in the mammalian auditory midbrain, the most studied of the vertebrates, and discuss how the mammalian auditory midbrain is functionally coordinated.

KEYWORDS: Auditory pathway, midbrain, inhibitory neural circuits, synaptic inputs

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Introduction

The auditory midbrains of vertebrates, besides being the first center in the auditory pathway, have several common features. First, in the auditory midbrain, frequency selectivity is spatially organized (tonotopic map). The vertebrate auditory pathway starts from the inner ear organs, where sound waves travel through the fluidic medium of the environment and are transformed into neural impulses. In the ear organ, different frequency information is coded by distinct neurons that are spatially aligned (tonotopicity). Then, the sound information is conveyed to the brainstem via the auditory nerve. In the brainstem, several nuclei send projections to the midbrain. Tonotopicity is preserved in most of these pathways and forms the frequency map in the auditory midbrain. Second, the auditory midbrain integrates information from the different auditory nuclei in the brainstem, where different nuclei form parallel auditory processing streams. Neurons in the midbrain do not receive input from a single source, but receive and integrate inputs from multiple nuclei. Third, the auditory midbrain is multimodal. In addition to audition, inputs from other sensory modalities (eg, somatosensory, visual, and electrical senses) are also integrated. This evidence suggests that the auditory midbrain is a common sensory processing center in vertebrates.

How is sensory information processed in the auditory midbrain? The auditory midbrain is comprised of intricate neural circuits, which receive inputs from ascending, descending, and intrinsic inputs. In the neurons of the auditory midbrain, multiple synaptic inputs are integrated and transformed into spike responses as an output. Thus, information processing is achieved through the integration of synaptic inputs. In particular, recent studies have shown that the interaction of the excitatory and inhibitory synaptic inputs is critical in shaping the neural response to sound in the auditory midbrain. Even in fish, inhibitory neural circuits in the midbrain are observed, suggesting that these circuits in the midbrain are very likely to be evolutionally old and essential for vertebrate hearing. In the first section of this review, we will provide a synopsis of the inhibitory circuits in vertebrates to reveal their common features. Details of the evolution of the vertebrate auditory system are, however, beyond the scope of this review. For more information, refer to the literature.[1–5]

In the second section, we will focus on the inhibitory circuits in the mammalian auditory midbrain. Mammalian auditory midbrain neural circuits are the most studied of the vertebrates and provide the most detailed information about the function and organization of these circuits. We will describe the organization of these inhibitory circuits on the basis of recent anatomical and physiological knowledge.

An Overview of the Inhibitory Neural Circuits in the Auditory Midbrain of Vertebrates

Electrophysiological studies have shown that neurons in the auditory midbrain of most vertebrates are shaped by inhibitory inputs. The source of these inhibitory inputs is thought to emanate from the auditory nuclei in the brainstem and the intrinsic inhibitory neurons in the midbrain. In Figure 1, we show the ascending auditory pathways to the vertebrate midbrain. In vertebrates, the basic auditory circuits in the brainstem consist of 3 main nuclei: the first-order nucleus that receives direct input from the inner ear; the second-order nucleus that receives inputs from the first-order nucleus; and the third-order nucleus that receives inputs from both first- and second-order nuclei. The first-order nucleus is obligatory, but the others are not. All of these nuclear groups send axons to the auditory midbrain. In mammals, the first-order nucleus

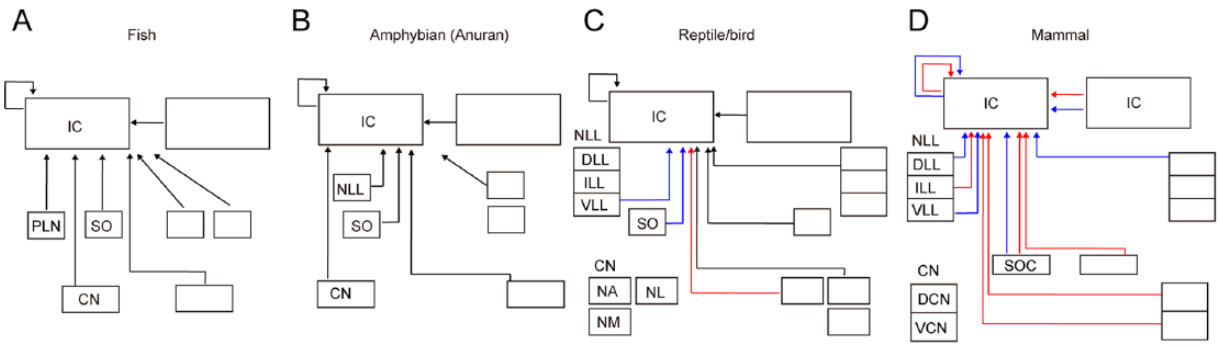

Figure 1. Schematic drawings of ascending auditory pathways to the vertebrate midbrain. Red and blue lines indicate excitatory and inhibitory pathways, respectively. The black lines indicate pathways in which the cell types of the projection neurons have not been identified. Thus, pathways indicated by the black lines are potentially either excitatory or inhibitory, or may contain both excitatory and inhibitory projections. We created these drawings based on the following literatures: (A) fish,[3,6–11] (B) anuran,[3,12–22] (C) reptile/bird,[23–37] and (D) mammals.[38–65] To emphasize the similarity in the basic organization of the auditory system, we used the terms CN, SO, NLL, and IC for first-, second-, third-order nuclei, and midbrain nucleus. CN indicates cochlear nucleus; DCN, dorsal cochlear nucleus; DLL, dorsal nucleus of lateral lemniscus; IC, inferior colliculus; ILL, intermediate nucleus of lateral lemniscus; NA, nucleus angularis; NM, nucleus magnocellularis; NL, nucleus laminaris; PLN, perilemniscal nucleus; SO, superior olive; SOC, superior olivary complex; VCN, ventral cochlear nucleus; VLL, ventral nucleus of lateral lemniscus.

is the cochlear nucleus (CN); the second-order nucleus is the superior olivary complex (SOC); and the third-order nucleus is the lateral lemniscus (NLL). Although the homology of the lower brainstem nuclei has not been established in all vertebrate clades, the basic organization of the auditory system (first-, second-, third-order nuclei and the midbrain) is shared among vertebrates. In this review, to emphasize the similarity of the organization and for simplicity, we use the terms CN, SOC (or superior olive [SO]), and NLL for the first-, second-, and third-order nuclei, respectively.

Although the basic organization of auditory pathways is similar, the detailed pattern of neural connections in the brainstem differs among classes and, with the exception of mammals, much is still unknown about the details of the connections. In particular, it is unknown whether the afferent inputs to the midbrain from the brainstem nuclei are excitatory or inhibitory. In the following sections, we will briefly describe the neural circuits in the auditory midbrain of non-mammalians.

Fish

Basic neuronal circuitry related to "audition" was likely present before the evolution of pure "hearing." Even aquatic anamniotes, which lack a specialized ear, can perceive sound from the movement of water through the inner ear, even without a cochlea. These inner ear organs are likely to exhibit both auditory and vestibular functions, as the vestibular organ responds to low-frequency particle motion elicited by both head movement and sound waves.[66] The sound and balance information that is perceived by the inner ear is transmitted to the brain through the octaval nerve. Aquatic anamniotes possess a lateral line system: the mechanosensory lateral line also perceives the movement of water and transmits through the lateral line nerve. The electrical sense organ has evolved in several anamniote clades independently from the mechanosensory lateral line organ. The receptor cells for both the lateral line and inner ear are hair cells, suggesting a common origin. Accordingly, lateral line and octaval systems share central pathways to a considerable degree. The fibers from the lateral line and inner ear terminate in columnar structures in the medulla, ie, lateralis and octaval columns, the reticular formation, and the cerebellum. Among them, the descending octaval nucleus, a homolog of the CN in mammals, is the main auditory region and is composed of several nuclei with various cell types that extract particular aspects of sound. To emphasize homology, we will refer to the primary auditory nucleus as CN. The axons from the lateralis and octaval columns cross the midline, pass through the contralateral lateral lemniscus, and terminate in the torus semicircularis, homologous to the inferior colliculus (IC) in mammals, of the midbrain roof or tectum. Again, emphasizing homology, we will refer to the auditory midbrain structure as IC. The IC also receives afferent inputs from the secondary octaval nucleus, SO, and the perilemniscal nucleus.[6,7]

Several physiological recordings have suggested that inhibition is critical in shaping the response properties of IC neurons in fish. In some IC neurons of the Mormyridae, the spontaneous spike activities are suppressed by sound.[67] Furthermore, it was found that IC neurons in oyster toadfish had sharper directional tuning than the primary saccular afferents and neurons in the descending octaval nucleus and the tuning is likely shaped by inhibitory processes.[11] However, the source of the inhibitory inputs in the IC is still unclear. An anatomical study has shown that the descending octaval nucleus, SO, and IC contain γ-aminobutyric acid (GABA)-positive neurons.[8] Although GABAergic neurons in the descending octaval nucleus were shown to have projections to the same nucleus of the contralateral side,[8,9] the innervation pattern of the GABAergic neurons to the IC is unknown.

Amphibian

The amphibian auditory pathway in the brainstem differs between anurans and nonanurans (urodeles and apodans).[3] Because there is little information about the auditory circuits in nonanurans, we have focused on the circuits of anurans. The auditory midbrain of anurans, the IC, receives ascending afferent inputs from the dorsal lateral nucleus, superficial reticular nucleus, and SO (Figure 1B).[3,12–14] The dorsal lateral nucleus and superficial reticular nucleus are the first- and third-order nuclei, designated CN and NLL, respectively. It is well known that anurans have acoustic social communication (eg, advertisement call of males), and it has been proposed that their auditory midbrain is a critical neural structure linking sensory inputs to behavioral responses.[14] Consistent with this view, in the midbrain of the anurans, the neurons have selective sensitivity to specific call features, some of which have been shown to be shaped by inhibition.[69–72] Of these, several in vivo whole-cell studies have clearly shown that the temporal interaction of the excitatory and inhibitory synaptic inputs were critical in shaping the sensitivities to the duration,[70,72] and the repetition rate[71] of sound of sound. However, as in the case of fish, the source of the inhibitory inputs is still unclear. Immunohistochemical studies show that GABAergic neurons are present in the CN, SO, NLL, and IC.[15] In addition to GABAergic neurons, the CN is likely to contain glycinergic neurons.[16,68] An in vitro physiological study showed that auditory nerve stimulation evoked both excitatory and inhibitory postsynaptic potentials (EPSP and IPSP) in IC neurons.[17] The short latencies of some IPSPs in the study[17] might suggest direct inhibitory inputs from the CN to the IC.

Reptile/bird

Reptiles and birds are both sauropsids, and share common organization of the auditory system.[4,24–26] Sauropsids' CN consists of 2 nuclei (Figure 1C): the nucleus angularis (NA) and the nucleus magnocellularis (NM). The NA projects to the SO, the nuclei of the lateral lemniscus (NLL), and the auditory midbrain (Figure 1C).[23,27] The NM projects to the second-order nucleus laminaris (NL).[26,73,74] NL is the first binaural station in the brainstem of sauropsids and detects the interaural time difference (ITD).[1,75,76] The NL projects to the SO, NLL, and the auditory midbrain.[23,27] The auditory midbrain in sauropsids is called the torus semicircularis, nucleus mesencephalicus lateralis dorsalis, or IC. Among sauropsids, the auditory system of the bird is well studied, so we will focus on avian findings. In the avian brainstem, several physiological studies show that inhibitory synaptic transmission has both GABAergic and glycinergic components.[77–80] In the NA,[77] NM,[78,80] NL,[80] and SO,[79] the inhibitory terminals co-release GABA and glycine. However, it is still unknown whether these transmitters are also co-released in the avian midbrain. In contrast to physiological studies, anatomical studies on inhibitory auditory neurons in the avian brainstem and midbrain are limited. Carr and colleagues[28] reported that GABAergic neurons were found in the midbrain and in many auditory nuclei in the brainstem. In the IC, GABAergic neurons are subdivided into 2 classes, large and small GABAergic (LG and SG) neurons, which are described in mammals (see Ito and Atoji[81]). Among the brainstem nuclei, the SO and NLL contain numerous GABAergic neurons and are most likely to send inhibitory inputs to the midbrain.[29,30] Of the NLL, the dorsal and ventral NLL (DLL and VLL, respectively) were shown to project to the midbrain.[30] The DLL is divided into anterior and posterior parts, which receive information relating to the ITD and the interaural level difference (ILD) from the NL and NA, respectively.[31,82] The VLL receives inputs from both the NL and NA and supposedly responds to binaural sound,[31] although a physiological study reported that all the VLL neurons were monaural.[82] In a chicken, in addition to GABAergic projections, the ipsilateral SO and VLL send glycinergic projections to the midbrain.[83] In reptiles, the SO and NLL contain numerous inhibitory neurons and are likely to project to the IC.[32]

Studies of barn owls have demonstrated that they have an auditory space map in the auditory midbrain: in the external nucleus of the IC, the neurons with preference to sound from specific locations are systematically aligned and form a map of the auditory space.[84–86] Inhibition plays a critical role in the formation of the auditory space map. The spatial tuning of the neurons in the external nucleus of the IC is shaped by the integration of the information of the ITD and ILD, which is then processed in parallel pathways in the brainstem and converges in the midbrain.[84,86] Inhibitory processes in the local circuits of the midbrain have been shown to affect the ITD and ILD selectivity of these neurons.[87–89]

Ascending Neural Circuits to the Mammalian Auditory Midbrain

The auditory midbrain of mammals will be termed the IC.[90] As with previously mentioned vertebrates, inhibition plays a critical role in shaping the neuronal response properties to sound (see the next section) in the mammalian IC, making it an essential process in the auditory midbrain of vertebrates. How are inhibitory neural circuits in the auditory midbrain conserved among the vertebrate clades? There are 2 common inhibitory inputs to the auditory midbrain in all vertebrates: the intrinsic inhibitory neurons in the auditory midbrain and those in the SO (Figure 1), although in mammals the SO is substituted by the SOC, a large nuclei complex that has evolved exclusively in mammals. Furthermore, in all vertebrates but fish, the NLL are a substantial source of the inhibitory projections to the auditory midbrain. Birds and mammals also share similar intrinsic inhibitory neuronal types (LG and SG neurons). These similarities suggest that the basic inhibitory neuronal circuits in the auditory midbrain could have formed in vertebrates in early evolutionary stages and were conserved through later stages. If the NLL in fish are shown

to be inhibitory and innervate the midbrain, this idea would be further supported.

Inhibition Is Critical in Shaping the Responses of Mammalian IC Neurons to Sound

Numerous electrophysiological studies have shown that inhibition plays a critical role in shaping the response properties of mammalian IC neurons to sound. Pharmacologic studies revealed that blocking inhibitory transmitters changes the various response properties of IC neurons to sound: frequency tuning,[91,92] firing rate,[93–95] temporal response patterns,[94,96] response latencies,[97] adaptation,[98,99] the sensitivities to amplitude[100] or frequency[101] modulation, and binaural processing.[94,102–106] Furthermore, recent in vivo whole-cell recordings showed that virtually all IC neurons received both excitatory and inhibitory synaptic inputs evoked by sound,[107] the interaction of which predominantly determined the response of the IC neurons to sound.[108] In most IC neurons, the excitatory and inhibitory synaptic inputs temporally overlap, and the temporal pattern of overlapping, as well as the ratio between excitatory and inhibitory inputs, is critical in shaping the temporal pattern of the spike responses.[107] Interestingly, the inhibitory inputs were not only observed in evoked responses during the sound stimuli but also in response at sound termination,[94,107,109] which might help in coding the endpoint of the sound. In addition to the temporal overlap, the excitatory and inhibitory inputs to the IC neurons also overlap in the frequency response area (FRA).[110,111] In most IC neurons, the FRA of the inhibitory inputs was broader than that of excitatory inputs.[110,111] The inhibitory inputs are most likely sharpening the FRA of spike responses. Consistent with this finding, the synaptic inputs in the IC were shown as having more broadly tuned FRAs than spike responses.[109] Furthermore, several in vivo whole-cell recordings elucidated the excitatory and inhibitory synaptic inputs underlying the binaural sound processing in the IC. In extracellular recordings, more IC neurons showed excitation to contralateral sound and inhibition to ipsilateral sound. However, in vivo whole-cell recordings in bats and mice showed that most IC neurons had excitatory and inhibitory synaptic inputs to both contralateral and ipsilateral sounds, whereas the excitatory inputs to ipsilateral sound were in the minority.[110,112,113] These studies also showed that the ILD sensitivity of IC neurons is inherited via excitatory inputs and sharpened by inhibitory inputs.[110,112,113] In addition to responses to pure tones, the responses to time-varying sounds were also processed by inhibition in the IC. The selectivity of IC neurons to frequency-modulated (FM) sounds was sharpened[114,115] or generated de novo[111] by the inhibitory inputs. This evidence suggests that inhibition essentially enhances the feature detection of the IC neurons.

What, then, is the source of inhibition in the mammalian IC? The neurons in the mammalian IC receive inhibitory inputs from the IC's intrinsic GABAergic neurons and ascending inputs. Following, we will describe the intrinsic and ascending inhibitory circuits of the mammalian IC.

Inhibitory Neurons Inside the IC

In the mammalian IC, there are no glycinergic neurons and all inhibitory neurons express GAD67 and show a GABAergic phenotype.[38–40] The GABAergic neurons in the IC are approximately 20%[39,41] and the remaining 80% are glutamatergic.[116] The GABAergic neurons are subdivided into several populations based on the presence of dense axosomatic rings of excitatory synapses and/or the presence of perineuronal nets, which are composed of extracellular matrix[42,117,118] (Figure 2A). GABAergic neurons with larger cell bodies (referred to as LG cells) tend to have both dense axosomatic excitatory synapses and perineuronal nets, and project to the medial geniculate body (MGB).[42] GABAergic cells with smaller cell bodies (referred to as SG cells) and glutamatergic cells lack pericellular specializations and do not make massive projections to the MGB. Dense axosomatic excitatory inputs on LG cells may help to securely elicit action potentials if they are driven simultaneously. Indeed, in the dorsal cortex of the IC, LG cells show a smaller latency than other cells in response to sound stimuli.[119] LG cells have thick axons that enter the brachium of the IC and terminate in the MGB.[43] Consistently, after stimulation of the brachium, an inhibitory response is elicited faster than an excitatory response in the MGB.[120] Such dual ascending projections of excitatory and inhibitory neurons may cause an interaction of inhibitory and excitatory postsynaptic potentials, producing de novo temporal response patterns in the MGB. As temporal information is particularly important for the auditory system, the interaction may aid analysis of temporal information, such as frequency and amplitude modulation.

The 3 cell types in the IC (LG, SG, and glutamatergic cells) are found in many amniote species, including the chicken, pigeon, bat, rat, mouse, common marmoset, and Japanese macaque.[81,44,45,123,124] This strongly suggests that the organization of cell types in the IC evolved at least 300 million years ago when the common ancestor of reptiles and mammals (stem amniotes) emerged. At this point, there is no information about the presence of the 3 cell types in the anamniote IC.

In most fish species, the IC homolog, the torus semicircularis, is present, whereas in electric fish, the IC is hypertrophied and shows specialization for electrical sense.[125] It would be interesting to test whether electrical sensory region of the IC consists of the 3 cell types that are found in amniote IC.

Inhibitory Ascending Projection to the Mammalian IC

The IC receives massive inhibitory ascending and excitatory inputs.[45,46] In mammals, ascending inhibitory inputs originate from the SOC and the NLL (Figure 1D). Within the SOC, the superior paraolivary nucleus, medioventral periolivary

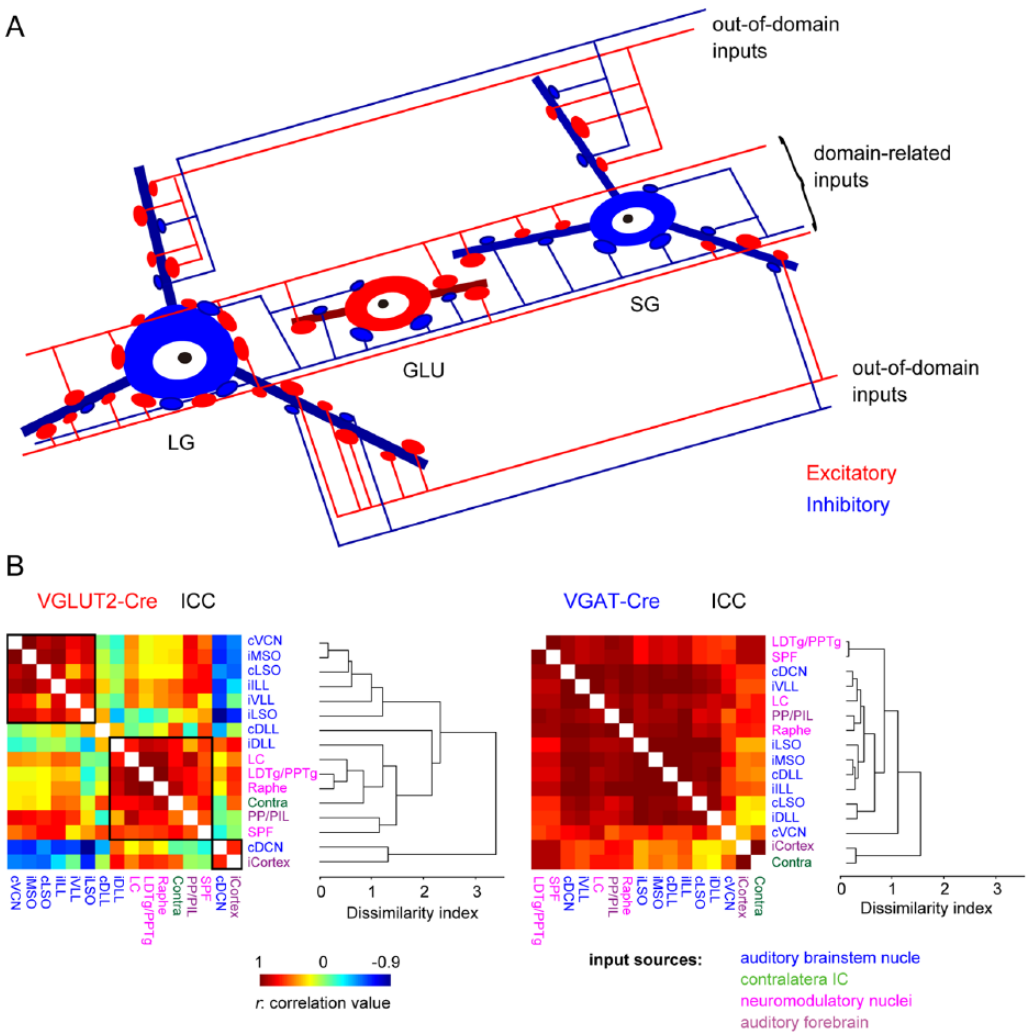

Figure 2. The combination of input sources is cell-type dependent. (A) The IC is composed of synaptic domains, which receive specific combinations of input nuclei.[55] A cell type–specific monosynaptic tracing study suggests that glutamatergic neurons (GLU, red) receive domain-specific inputs, whereas GABAergic neurons (LG and SG, blue) receive similar combinations of inputs which are unrelated to the location of cell bodies.[53] However, excitatory axosomatic inputs to LG neurons are location-dependent.[121] Consistent with this fact, GABAergic neurons show a responsiveness to sound that is similar to the responsiveness of adjacent GLU neurons.[122] Both LG and SG neurons have a large dendritic field that covers several synaptic domains, whereas GLU neurons have a smaller dendritic field (Ito, unpublished observation). Out-of-domain neurons may receive different input nuclei, and as a consequence, the net inputs to GABAergic neurons would be similar and unrelated to the location of the somata. The out-of-domain inputs may contribute subthreshold responses to sound and make GABAergic neurons state-dependent. (B) The combination of input nuclei is location-dependent inside the central nucleus of the IC (ICC) for GLU neurons (top), whereas it is always similar and unrelated to the location inside the ICC for GABAergic neurons (bottom). Cre-dependent monosynaptic retrograde tracing was examined for VGLUT2-Cre and VGAT-Cre mice, which express Cre in GLU and GABAergic neurons, respectively, in the IC. Inputs per starter neurons were calculated for each input nuclei; a correlation of the ratios between input nuclei was obtained for all pairs of input nuclei, and heat maps of correlations were shown on the left. Dendrograms of the dissimilarity of correlation were made to examine the presence of clusters of similarity. In GLU neurons, 3 clusters of correlated nuclei were visible, namely, the cluster composed of auditory brainstem nuclei, composed mainly of neuromodulatory nuclei, and those composed of the contralateral (c) dorsal cochlear nucleus (DCN) and ipsilateral (i) auditory cortex (Cortex). This suggests that the combination of input nuclei is related to the injection sites of the tracer. However, GABAergic neurons exhibited a high correlation among all pairs of input nuclei, suggesting that the combination of input nuclei is always the same. IC indicates inferior colliculus; LC, locus coeruleus; LDTg/PPTg, laterodorsal and peduculopontine tegmental nuclei; LG, large GABAergic; PP/PIL, peripeduncular and posterior intralaminar thalamic nuclei; SG, small GABAergic; SPF, subparafascicular nucleus; VCN, ventral cochlear nucleus.
Adapted from Chen et al.,[53] with permission from the *Journal of Neuroscience*.

nucleus, and lateral superior olive (LSO) are the main sources of inhibitory projections.[47,48] Inhibitory neurons in these nuclei project to the ipsilateral IC. The superior paraolivary nucleus and the medioventral periolivary nucleus are composed of monaural neurons, which fire at the termination of the sound stimulus and are sensitive to the temporal structures of sound.[126,127] These nuclei, therefore, are likely to be the source of the inhibitory inputs at the termination of the sound stimulus. The LSO conveys binaural information to the IC. The neurons in the LSO are excited by ipsilateral sound and inhibited by contralateral sound and code for ILD.[128] The LSO sends the inhibitory and excitatory projections to the ipsilateral

and contralateral IC, respectively[47,49]; therefore, the IC neurons with LSO inputs are excited by contralateral sound and inhibited by ipsilateral sound. Consequently, ILD coding in the LSO is passed on to the IC. In the NLL, the DLL and VLL are the main sources of inhibition to the IC.[48,50] The DLL projects bilaterally while the VLL projects ipsilaterally to the IC.[47] The DLL is composed of binaural neurons which are excited by contralateral sound and inhibited by ipsilateral sound.[129] Most of the VLL neurons are monaural and they tend to show broad frequency tuning and high sensitivity to the temporal structure of sound.[130] The monaural nuclei of the lateral lemniscus are hypertrophied in echolocating bats, and it is suggested that they are involved in measuring the distance to a target using the delay of echoes from sonar pulses.[131] In most of these nuclei, neurons co-express GAD67 and GLYT2, markers for GABAergic and glycinergic neurons, respectively,[44,51] and they have been shown to co-release GABA and glycine.[132] The exception is the DLL, which expresses GAD67, but not GLYT2. Thus, the ascending inhibitory inputs to the mammalian IC are both GABAergic and glycinergic. In addition to these inhibitory inputs from the brainstem, it was anatomically verified that the neurons in the mammalian IC received inhibitory inputs from both the ipsilateral[123] and contralateral sides.[52,53]

Different Patterns of Afferent Inputs Between Excitatory and Inhibitory Neurons in the IC

The IC receives inputs from various sources: auditory inputs come from almost all auditory brainstem nuclei and the contralateral IC. Most descending inputs originate from the auditory cortex, and a smaller portion originates from the non-lemniscal auditory thalamus.[133] The IC also receives multimodal sensory inputs from the retina, dorsal column nuclei, and spinal trigeminal nucleus.[134–136] Activity of the IC is modulated by various neuromodulators, eg, acetylcholine, dopamine, and serotonin. These inputs from various sources do not mix homogenously in single IC neurons, but separately terminate into different synaptic domains. Indeed, it has been shown that the lateral part of the central nucleus of the IC (ICC) receives inputs mostly from the LSO and the medial superior olive (MSO), whereas the medial and caudal parts of the ICC receive the bulk of inputs from cochlear nuclei. The IC cortex receives fewer inputs from the LSO, MSO, or CN.[54,137] However, these studies did not show how the afferent inputs are different among cell types. In a recent study,[53] using cell type–specific monosynaptic retrograde tracing, the authors demonstrated that the combination of afferent inputs is different between GABAergic inhibitory neurons and glutamatergic excitatory neurons. In glutamatergic neurons, neurons in different locations receive different combinations of inputs: inputs from some nuclei show a positive correlation to other nuclei and there are clusters of input nuclei that show a positive correlation to each other. In the ICC, there are 3 clusters that are mainly composed of ascending, modulatory, and descending nuclei (Figure 2B). In the IC cortex, there are two clusters; one is composed of ascending nuclei, whereas the other is composed of modulatory and descending inputs. Interestingly, regardless of location, GABAergic neurons receive similar combinations of inputs. This strongly suggests that the neuronal circuitry of GABAergic neurons is very different from that of glutamatergic neurons.

Sound Response Properties of the Excitatory and Inhibitory Neurons in the IC

Using transgenic animals which express channelrhodopsin 2 in inhibitory neurons, recent studies optogenetically identified glutamatergic and GABAergic neurons in vivo in the mouse IC[122,138] and compared sound response properties.[122] The comparison showed that the 2 classes of neurons displayed differences in their spontaneous activities: GABAergic neurons had a higher rate of spontaneous activity than glutamatergic neurons (Figure 3A). However, concerning response properties to pure tone, both cell classes had as a whole, similar thresholds, response latencies, rate-level functions, and frequency tuning. Furthermore, response properties of both cell classes were affected by their location in the IC and neurons in nearby circuits shared similar frequency tunings (Figure 3A) regardless of cell type (Figure 3B).[122] It is proposed that the mammalian IC is composed of a number of microdomains ("synaptic domains") which receive particular combinations of inputs from extrinsic sources.[55,137] In these microdomains, neurons are likely to receive a similar set of afferent synaptic inputs so that they share similar response properties to sound (Figure 3C). The similarity of the response properties of GABAergic and glutamatergic neurons suggests that they might receive similar afferent inputs in local circuits. However, this seems inconsistent with the anatomical observation that GABAergic and glutamatergic neurons had distinct patterns of afferent inputs in local circuits[53] (Figure 2). This discrepancy might be explained by differences in dendritic morphology between glutamatergic and GABAergic neurons. Glutamatergic neurons have compact dendritic fields, whereas the SG and LG neurons have broad dendritic fields (Ito, unpublished data). Thus, compared with glutamatergic neurons, GABAergic neurons are more likely to receive diverse synaptic inputs beyond microdomains. However, the synaptic inputs at the distal dendrite might be attenuated along the dendritic process[139,140] and have less impact on sound-evoked spike response than synaptic inputs at the proximal dendrite within the microdomains (Figure 2). Still, distal inputs can affect spike generation depending on the state of the neuron. For example, when the resting potential is enhanced by neuromodulator inputs, the neuron would be more easily affected by attenuated distal inputs. Spike generation would also be enhanced by distal inputs when they are synchronized with proximal inputs. This synchronization can be induced by broadband noise or FM sound.

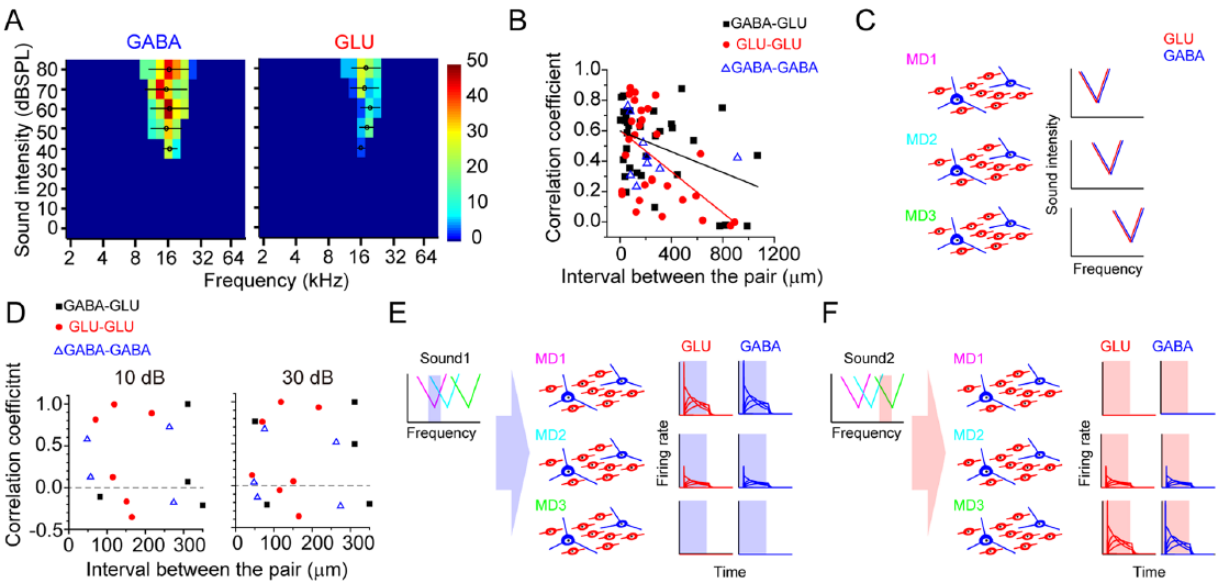

Figure 3. The sound response organization in the microdomain. (A) The FRAs of closely located GABAergic (left) and glutamatergic (right) neurons. (B) The correlation coefficient of the FRAs of paired neurons was plotted against the distance between the neurons. Closely located neurons had higher correlation coefficients of the FRAs, regardless of the cell types. (C) The schematic drawing of the FRA organization in the microdomains. The different frequency channels might be shaped by different microdomains, in which the excitatory and inhibitory neurons shared similar FRAs. (D) The correlation coefficients of peristimulus time histograms (PSTHs) of closely located neurons. The correlation coefficient was plotted against the distance between the pair. Each panel represents the response to a different sound intensity (10 and 30 dB above threshold). The schematic drawings of the outputs from the microdomains in the response to sounds: (E) Sound 1 (low-frequency sound) evokes responses in the low- and middle-frequency regions (MD1 and MD2), but not in the high-frequency region (MD3). Both excitatory and inhibitory outputs from the microdomains contain diverse temporal spike sequences. The red and blue traces in the right panels represent excitatory and inhibitory PSTHs of neurons in a microdomain. (F) Sound 2 (low-frequency sound) evokes responses in the middle- and high-frequency regions (MD2 and MD3), but not in the low-frequency region (MD1). FRA indicates frequency response area.

Adapted from Ono et al.,[122] with permission from the *Journal of Neuroscience*.

Unlike frequency tunings, temporal patterns of the responses were not shared in the local circuits (Figure 3D). A previous study showed that the temporal patterns of the responses of IC neurons reflected the time course of the excitatory inputs.[107] Thus, afferent inputs in the IC microdomain might contain excitatory inputs with different temporal patterns. Nevertheless, they have similar frequency tunings. These results suggest that each microdomain might work as a distinct frequency channel (Figure 3C), and, when the preferred frequency sound is given, it may generate both excitatory and inhibitory outputs that contain diverse temporal spike patterns (Figure 3E and F). It has been proposed that in the sensory neocortex, neurons in the local circuit generate spikes with different time courses, which then form a sequentially structured population activity (packet).[141,142] The packet activity in the sensory cortex was conserved when the stimulus varied[141] and might create a stable transfer of information between the brain regions.[142] The diversity of the responses in the temporal patterns of the IC microdomain might generate similar sequentially structured neuronal outputs.

Furthermore, glutamatergic and GABAergic neurons had different responses to amplitude-modulated (AM) sound: glutamatergic neurons could follow AM sound with a higher modulation rate compared with GABAergic neurons, even when the envelope shape was sharp. This difference might reflect differing membrane properties between these cell types. It has been reported that GABAergic IC neurons have a longer afterhypolarization and a slower membrane time constant than the glutamatergic IC neurons.[40] These membrane properties might limit the ability of the GABAergic neurons to rapidly follow varying synaptic inputs evoked by fast AM sound.[143] These results are in contrast to sensory cortices where interneurons are hypothesized to pool local excitation[144] and have broad tuning properties.[145–148] The similar properties of GABAergic and glutamatergic neurons in local circuits might suggest the unique functional organization of the IC. However, to understand the functions of the GABAergic and glutamatergic neurons in the IC, it is necessary to elucidate how the excitatory and inhibitory outputs of the IC are processed in postsynaptic neurons. For this purpose, it is necessary to identify the response properties of the LG and SG, which are GABAergic projection neurons and assumed interneurons, respectively. It will also be necessary to reveal the innervation patterns of LG, SG, and glutamatergic neurons.

Disinhibitory Circuitry in the Ascending Auditory Pathway

As shown above, the IC receives massive inhibitory inputs from multiple lower brainstem auditory nuclei and sends ascending inhibitory efferents to the MGB. The monosynaptic

retrograde tracing study[53] suggests that some inhibitory afferents are likely to be coupled with inhibitory efferents: GABAergic neurons in the ICC receive more inhibitory inputs from the VLL than glutamatergic neurons. It is possible that the activity of the VLL inhibits LG neurons and causes disinhibition in neurons in the MGB. More interestingly, ICC GABAergic neurons are more heavily innervated by putative serotonergic neurons in the raphe nuclei than glutamatergic neurons, whereas they are more weakly innervated by putative dopaminergic neurons in the subparafascicular nucleus than are glutamatergic neurons. This suggests that dopamine and serotonin act differentially on glutamatergic and GABAergic pathways, respectively, and serotonin modulates the activity of GABAergic neurons and changes the mode of disinhibition.

There is yet another disinhibitory pathway in the IC. GABAergic neurons in the IC cortex preferentially receive inhibitory inputs from the contralateral IC cortex.[53] Therefore, inhibitory neurons in the IC cortex of one side are reciprocally connected with those in the other side through the commissure of the IC. As dense clusters of GABAergic neurons in the IC cortex receive somatosensory inputs[149] and send axons to the periaqueductal gray (PAG),[53] somatosensory inputs to one side may inhibit the GABAergic neurons on the other side and release the inhibition on the PAG. As projections from the IC cortex to the PAG are related to innate escape behaviors,[150] the multimodal commissural disinhibitory projection may act to trigger some behaviors.

Conclusions

The auditory midbrain is the computational center of the auditory pathway in vertebrates. In the auditory midbrain of all vertebrates, synaptic inhibition is critical to information processing. Thus, the inhibitory neural circuits in the auditory midbrain may have formed in the early stages of vertebrate evolution. The basic structure of the inhibitory circuits appears to be preserved among vertebrates. In the mammalian IC, virtually all neurons receive temporally overlapping excitatory and inhibitory inputs, whose interaction predominantly determines neural response properties. The mammalian IC contains glutamatergic and GABAergic neurons. GABAergic neurons are classified into SG and LG, which are assumed to be local interneurons and projection neurons, respectively, and form different neural circuits. The glutamatergic and GABAergic neurons in the IC are reported to share similar frequency tunings in local circuits and are affected by microdomains in the IC. Conversely, a study of cell type–specific monosynaptic retrograde tracing suggests that the glutamatergic and GABAergic neurons have different neuronal circuits. GABAergic neurons receive inputs from various sources, whereas glutamatergic neurons receive a combination of inputs, which are determined by the location of the somata. Both cell types mainly receive the input of different neuromodulators. Thus, it is possible that response properties of single GABAergic neurons could be state-dependent and more variable than single glutamatergic neurons. These recent findings suggest that the functional organization of the IC is unique in the auditory pathway and is different from sensory cortices.

Author Contributions

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