Functional organization of the mammalian auditory midbrain

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Abstract The inferior colliculus (IC) is a critical nexus between the auditory brainstem and the forebrain. Parallel auditory pathways that emerge from the brainstem are integrated in the IC. In this integration, de-novo auditory information processed as local and ascending inputs converge via the complex neural circuit of the IC. However, it is still unclear how information is processed within the neural circuit. The purpose of this review is to give an anatomical and physiological overview of the IC neural circuit. We address the functional organization of the IC where the excitatory and inhibitory synaptic inputs interact to shape the responses of IC neurons to sound.

Keywords Inferior colliculus • Local circuit • GABAergic neuron • Membrane property • Synaptic inputs

Abbreviations

IC Inferior colliculus
CN Cochlear nuclei
SOC Superior olivary complex
NLL Nucleus of the lateral lemniscus
VCN Ventral CN
DCN Dorsal CN
LSO Lateral superior olive
ILD Interaural level difference
MSO Medial superior olive
ICC Central level difference
MGB Medial geniculate body
LG Large GABAergic
VGLUT Vesicular glutamate transporter
$R_i$ Input resistance
SR Sustained regular
MNTB Medial nucleus of the trapezoid body
LNTB Lateral nucleus of the trapezoid body
DNLL Dorsal NLL
VNLL Ventral NLL

Introduction

The IC is located in the midbrain and is believed to be the first integration center in the auditory pathway. Almost all auditory information is conveyed, integrated, and processed in the IC before being sent to a higher auditory center. Inside the IC neural circuit, auditory information is transformed. The general rules of this transformation have not been fully established, because of incomplete knowledge of the neural circuit in the IC. Here, we discuss the functional organization of the IC to aid our understanding of how the IC processes auditory information. This review focuses on the mammalian auditory system (other clades are discussed elsewhere [1, 2]) We first describe the anatomical and synaptic organization of the IC neural circuitry, then discuss two critical physiological aspects of information processing by the IC neural circuit: the diverse membrane properties of postsynaptic neurons and the convergence of excitatory and inhibitory synaptic inputs.
An overview of the mammalian auditory pathway

Sound is transformed into neural signals in the cochlea, in which the frequency of sound is analyzed (Fig. 1a). Auditory information, for example the spectrum, timing, and location of sound is analyzed in parallel in the lower brainstem nuclei, i.e., cochlear nuclei (CN), superior olivary complex (SOC), and nuclei of the lateral lemniscus (NLL, Fig. 1a). For example, T-stellate neurons in the ventral cochlear nucleus (VCN) can convey sound spectra over a wide range of sound intensity [3]. Fusiform cells in the dorsal cochlear nucleus (DCN) code sound intensity and spectrum in a complex frequency response area and are believed to be the analyzers of spectral cues that are created by the head and pinnae and are necessary for sound location [3]. Neurons in the lateral superior olive (LSO) code interaural level differences (ILD) whereas those in the medial superior olive (MSO) code interaural time difference. Both are necessary for analysis of sound location in space [4]. The dorsal NLL (DNLL) is one of the major sources of GABAergic input to the IC [5]. All of these brainstem structures project to the IC [6]. These projections include both the excitatory and inhibitory inputs to IC (Fig. 1a). These basic patterns of connection from the

Fig. 1 The neural circuit of the inferior colliculus. a Schematic diagram of main inputs to the IC of mammals. Red, blue, and green arrows indicate glutamatergic, GABAergic, and glycinegic projection. DNLL dorsal nucleus of the NLL, INLL intermediate nucleus of the NLL, VNLL ventral nucleus of the NLL. b A model of synaptic organization of the ICC. Each functional module is denoted by a different shade and represents a different excitatory brainstem input (red, ipsilateral MSO; blue, contralateral DCN; green, contralateral LSO). Inhibitory inputs (ipsilateral LSO, yellow spheres; DNLL, blue spheres) terminate in particular domains and avoid others. The distribution of some modules is highly related to the tonotopic map (stacked laminae inside the ICC), because some inputs are absent at the ends of the frequency ranges. Within each lamina, disc-shaped neurons (shown in a red lamina) extend their dendrites. Adapted, with permission, from Ref. [6]. c Schematic diagram of neural circuitry in which LG neurons (blue cells) are involved. Inside the ICC, more ventral and medial domains receive dense ascending inputs from the DCN whereas the more lateral domain receives dense inputs from the SOC and NLL. LG neurons receive glutamatergic (red) inputs from local and ascending sources. Because local excitatory neurons innervate LG neurons located in different synaptic domains and those located in the same domain, an LG neuron may mix information from multiple synaptic domains. LG neurons may control specific local circuitry in the thalamus, because LG neurons innervate stellate neurons and a subpopulation of tufted neurons in the MGB (color figure online)
lower auditory nuclei to the IC are well-preserved among the mammalian clade [7].

**Functional structure of the IC**

The IC is subdivided into the central nucleus (ICC) and a surrounding cortex (Fig. 1b). Most of the ascending fibers from the lower auditory brainstem nuclei terminate in the ICC (Fig. 1a) [6]. The IC cortex receives inputs mainly from the ICC [8] and descending fibers from the cerebral cortex [9, 10], which suggests the IC cortex is involved in attention to sound. Interestingly, some neurons in the IC cortex can detect changes in the auditory scene [11]. In addition to the auditory inputs, the lateral cortex of the IC receives visual [12, 13] and somatosensory information [14], which suggests it may also be involved in multimodal integration.

The ICC has a characteristic anatomical organization characterized by fibrodendritic laminae that contain functional zones in different parts of the same layer [15–18]. Disc-shaped neurons have oriented dendrites that form fibrodendritic laminae with flattened plexuses of afferent axons [15] (Fig. 1b). These laminae are the basis of the tonotopic organization of the ICC, and the neurons in the same lamina share a similar best frequency [17, 19]. Although the fibrodendritic laminae that receive inputs share similar frequency tuning, the distribution of afferent inputs from the lower brainstem auditory nuclei is not homogeneous within a lamina. For example, DCN axons terminate in the more dorsomedial parts of the ICC laminae [20] whereas LSO axons terminate on the ventrolateral parts [21] (Figs. 1b, c). This distribution of ascending inputs on the laminae organizes ICC layers into synaptic domains, each of which receives a specific combination of ascending inputs from different brainstem nuclei [6, 18, 22] (Fig. 1b). Thus, in the same lamina, neurons that receive a different combination of afferent inputs will, accordingly, have a substantial differences in their responses to sound [18, 19, 23]. Fibrodendritic laminae and synaptic domains overlap each other and subdivide the ICC into local functional zones (Fig. 1b). In contrast to the ICC, the IC cortex is organized in several layers each of which has distinct input and output connections. The functional organization of the IC cortex is less well known than that of the ICC, but a recent imaging study showed that layer 1 of the dorsal IC cortex has region-specific frequency selectivity [24]. Layer 2 of the IC lateral cortex contains a periodic module composed of small GABAergic neurons (the GABA module, [25]) that have distinct intrinsic membrane properties [26] in GAD67-GFP knock-in mice [27].

**Synaptic organization of local circuit in the IC**

A unique feature of the IC is that it sends both excitatory and inhibitory projections [28, 29] to the medial geniculate body (MGB, Fig. 1a). IC neurons are either glutamatergic or GABAergic [26, 30], although many kinds of neurotransmitter are also expressed in the IC [31–34]. Tectothalamic GABAergic neurons have large somata and a distinctive synaptic structure [29]. Large GABAergic (LG) neurons are covered by numerous axosomatic and axodendritic excitatory terminals. LG neurons are found in a variety of mammalian species (rats, mice, rabbits, bats, and monkeys; unpublished data), suggesting the IC GABAergic neural circuitry is widely preserved among mammals. Calyx-like or endbulb-like synapses have not been found in the IC, and LG neurons have been shown to receive converging inputs from multiple axons from different sources [35–38]. The excitatory axosomatic terminals on LG neurons are positive for vesicular glutamate transporter (VGLUT) 2 but not for VGLUT1 [29], and originate from neurons which express VGLUT2 in the brainstem (DCN, SOC, NLL) and in the IC itself [37, 38]. For example, a single IC excitatory neuron can form an axonal plexus parallel to and within a fibrodendritic lamina and make axosomatic contacts with 10–30 LG neurons within the plexus over a distance of several hundreds of microns. Therefore, the fibrodendritic lamina is the field of convergence for local and ascending axonal inputs. Along a single fibrodendritic lamina, the density of terminals from each ascending source is not homogenous but separated into separate synaptic domains as described above (Fig. 1b). The local excitatory neurons may affect the LG neurons located in neighboring synaptic domains as well as in its own. This suggests that an LG neuron mixes ascending auditory information that it receives directly from ascending fibers with information received by neurons in the neighboring domains (Fig. 1c).

**Diverse physiological properties of IC neurons**

Previous whole-cell recording studies in the IC in vitro and in vivo showed there were neurons with distinctive firing properties (modeled discharge patterns are shown in Fig. 2a). They were classified into 6–8 types on the basis of the responses to depolarizing and hyperpolarizing currents (Fig. 2a) in mice, rats, and bats [26, 39–41]. It has been suggested that different expression patterns of potassium and calcium channels create these different firing types [26, 39]. IC neurons are also diverse in their input resistances ($R_i$, Table 1). In-vivo recordings from mature animals revealed that $R_i$ ranged from 30 to 450 MΩ (bat, ICC) [41].
and from 39 to 615 MΩ (mouse, IC cortex) [42]. The $R_i$ values in slice recordings were higher than those in vivo (Table 1), probably because of the immaturity of the tissue (see age in Table 1). $R_i$ was reported to be inversely correlated with somatic size (Table 1) [42] whereas firing types were not well correlated with morphology [26, 43]. Importantly, neurons with different membrane properties were heterogeneously mixed in the IC. No relationship was observed between neuronal membrane property and spatial distribution (except for GABA module neurons [26]). Thus, a synaptic domain in the ICC is likely to contain a mixture of neurons with different intrinsic membrane properties. Interestingly, recent studies using tetrode recordings showed that the correlation of the temporal responses with sound was usually low for closely located ICC neurons [19, 23] and the degree of the correlation of their frequency tuning depended on distance between neurons [19]. These results suggested there might be a

![Fig. 2 Firing types and synaptic responses of IC neurons.](image)

**Table 1** The input resistance ($R_i$) of IC neurons

| Cell type           | $R_i$ (MΩ)± | No. of cells | Species | Age   | Preparation | Ref. |
|---------------------|-------------|--------------|---------|-------|-------------|------|
| Sustained-regular (SR) | 393.45 ± 190.1 | 10           | Rat     | P8–17 | Slice       | [39] |
| Onset               | 643.71 ± 243.8 | 8            | Rat     | P8–17 | Slice       | [39] |
| Rebound             | 229.6 ± 88.0  | 19           | Rat     | P10–19| Slice       | [62] |
| SR-GABA             | 413.0 ± 239.6 | 69           | Mouse   | P12–31| Slice       | [26] |
| SR-nonGABA          | 280.7 ± 120.4 | 19           | Mouse   | P12–31| Slice       | [26] |
| All types           | 106 ± 51      | 103          | Mouse   | P21–37| In vivo     | [40] |
| Small (<15 µm)      | 214 ± 91      | 68           | Mouse   | P21–79| In vivo     | [42] |
| Medium (15–25 µm)   | 144 ± 53      | 35           | Mouse   | P21–79| In vivo     | [42] |
| Large (>25 µm)      | 82 ± 38       | 12           | Mouse   | P21–79| In vivo     | [42] |

$^a$ $R_i$ is given as mean ± standard deviation. When the original value was given with the standard error, the standard deviation was calculated from the standard error.
decorrelation in a synaptic domain that could increase coding capacity [44, 45]. Variability in the intrinsic membrane properties may contribute to decorrelation of the neural responses in the IC local circuit.

Compared with the neurons in the brainstem, the IC neurons have higher $R_i$ (Tables 1 and 2). Neurons with extremely low $R_i$ are seen in the brainstem nuclei (indicated with b in Table 2, i.e., VCN octopus neurons and MSO principal neurons) but not in the IC. Those low $R_i$ neurons are highly specialized for coincidence detection over a sub-millisecond timescale [46]. For these neurons, extremely short membrane time constant makes EPSP brief, so that firing requires highly coincident synaptic summation. The high $R_i$ of the IC neurons might make them less incapable of reproducing the temporal structure of their inputs with high fidelity compared with lower auditory brainstem neurons, and they are more likely to act as temporal integrators [47]. This notion is consistent with the observation that temporal synchronization to amplitude-modulated sound is degraded in the IC [48].

**Integration of excitatory and inhibitory synaptic inputs shapes tuning to sound in an IC neuron**

As shown above, anatomical studies have suggested that the synaptic inputs from different sources converge on an IC neuron. Reflecting their locations in different synaptic domains, IC neurons will receive synaptic inputs with different temporal patterns. Intracellular studies (cats, guinea pigs, and bats) have shown that interaction of excitatory and inhibitory inputs affects neural responses of IC neurons [49–52]. Recent in-vivo whole-cell recording of mice, rats, and bats have shown that virtually all the IC neurons receive excitatory and inhibitory synaptic inputs (Figs. 2b–e) [53–59]. Analysis of synaptic responses to binaural stimuli showed that many IC neurons receive inputs from several sources (Fig. 2b; note that contralateral and ipsilateral sounds evoked both excitatory and inhibitory responses) [54, 56, 59]. The excitatory inputs are temporally diverse and contribute substantially to the temporal pattern of action potential firing (Figs. 2c–e) [53, 55, 61]. Furthermore, the balance and timing of the excitatory and inhibitory inputs are crucial in shaping the spike responses [53, 55–59, 61]. Because the sound-evoked excitatory and inhibitory synaptic inputs temporally overlap (Figs. 2b–e), their relative size and timing affects spike generation profoundly [53, 58, 61] and determines the sound selectivity of the neuron [55–57, 61]. In binaural responses, nonlinear synaptic summation is also critically involved in shaping the selective responses to different binaural stimuli [54, 56, 59]. Nonlinear summation of monaural responses is observed for synaptic inputs; this sharpens selectivity to interaural level differences (ILD). Furthermore, extracellular and intracellular recordings from the same neuron showed that the ILD curve of spike responses was more sharply tuned than that of the synaptic responses (Fig. 2e). These observations suggest that the sound responses of IC neurons were determined by the complex interaction of synaptic inputs and postsynaptic processes that reflect the intrinsic membrane properties.

| Table 2 $R_i$ of auditory brainstem neurons |
|-------------------------------------------|
| **Nucleus** | **Cell type** | **$R_i$ (MΩ)$^a$** | **No. of cells** | **Species** | **Age** | **Ref.** |
|---------------|----------------|-----------------|-----------------|-------------|--------|----|
| VCN           | Bushy          | 40.2 ± 9.8      | 24              | Mouse       | P29–39 | [63]|
| VCN           | T-stellate     | 81.5 ± 36.7     | 21              | Mouse       | P29–39 | [63]|
| VCN           | D-stellate     | 60 ± 17         | 11              | Mouse       | P16–18 | [64]|
| VCN           | Octopus$^b$    | 6 ± 6           | 10              | Mouse       | P16–19 | [65]|
| DCN           | Fusiform       | 93.2 ± 49.5     | 21              | Mouse       | P15–25 | [66]|
| DCN           | Cartwheel      | 55.7 ± 18.6     | 5               | Mouse       | P16–24 | [67]|
| DCN           | Vertical       | 163.7 ± 53.8    | 27              | Mouse       | P16–23 | [68]|
| DCN           | Stellate       | 996 ± 749       | 29              | Mouse       | P15–32 | [69]|
| MSO           | Principal$^b$  | 10 ± 9          | 18              | Gerbil      | P17    | [70]|
| LSO           | Principal      | 23.4 ± 19.0     | 7               | Mouse       | P23    | [71]|
| MNTB          | Principal      | 80.6 ± 23.4     | 10              | Gerbil      | P19–22 | [72]|
| LNTB          | Principal      | 56.5 ± 33.7     | 50              | Gerbil      | P18–22 | [72]|
| VLL           | Globular       | 108.3 ± 36.2    | 7               | Gerbil      | P25<   | [73]|
| DLL           | Principal      | 137 ± 26        | 7               | Gerbil      | P23–26 | [5] |

$MNTB$ medial nucleus of trapezoid body, $LNTB$ lateral nucleus of trapezoid body

$^a$ $R_i$ is given as mean ± standard deviation. When the original value was given with the standard error, the standard deviation was calculated from the standard error

$^b$ The neurons with extremely low $R_i$ in the brainstem
Concluding remarks

The mammalian IC is an auditory center that transforms its afferent inputs into excitatory and inhibitory outputs within local functional zones. IC is characterized by a complex neural circuitry in which IC neurons with a variety of physiological properties reside in functional zones that receive different combinations of afferent inputs from different sources. This generates neurons with a great variety of responses to sound. This complexity and diversity makes it challenging to elucidating the function of the IC. To truly understand the function of the IC, we require more basic knowledge to distinguish the unique phenotypes of IC neurons in vitro and in vivo. It will be also an important to investigate common and different interspecies features of the physiological characteristics of IC neurons, because most current knowledge of the cellular physiology on IC neurons is based on recordings from rodents.

Acknowledgments We thank Dr Douglas L. Oliver (University of Connecticut Health Center) for critical reading the manuscript. This review is based on a symposium held during the Joint Meeting of the Japanese Association of Anatomists and The Physiological Society of Japan, where the speakers were M.O., T.I., and Drs Chen Chen, Yaneri Ayala, and Kazuo Funabiki.

Compliance with ethical standards

Funding This work was supported by grants from NIH R01 DC000189, R21 DC013822, UConn Health HCRAC grant 401139UCCH (to Dr D.L. Oliver), the Japan Society for the Promotion of Science (grants 22700365 and 25430034, T.I.), the Uehara Memorial Foundation (T.I.), the Ichiro Kanehara Foundation (T.I.), the Novartis Foundation for the Promotion of Science (T.I.), and Research and Education Program for Life Science of the University of Fukui (T.I.).

Conflict of interest The authors declare that they have no conflict of interest.

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