Dissecting the circuitry of the auditory system

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The brainstem auditory system is a complex system composed of numerous parallel and serial pathways that converge on a common destination in the inferior colliculus (IC). The exact nature of the response transformations that occur in the IC have, however, been elusive – even though the IC has been the subject of numerous studies for more than 30 years. Recent studies have addressed this issue by recording from IC neurons before and during micro-iontophoresis of drugs that selectively block $GABA_A$ or glycine receptors (the dominant inhibitory receptors in the IC) or by reversibly inactivating a lower nucleus that provides inhibitory innervation to the IC. These studies have revealed some of the ways that signals, relayed via many different parallel routes, interact in the IC, and suggest some functional advantages that these interactions might have.

Two of the primary goals of auditory neuroscience are to determine how acoustic information is progressively transformed along the auditory pathway and to understand the functional consequences of those transformations. These goals have been difficult to achieve, in large part owing to the complexity of the auditory system. The ascending auditory system is composed of a large number of nuclei connected through a series of parallel pathways. The pathways begin with the auditory nerve, which branches to distribute information to the various cell groups in the cochlear nucleus (Fig. 1). Each cell group in the cochlear nucleus transforms the incoming spike trains uniquely [1] and then distributes that information along a series of parallel pathways to a myriad of auditory nuclei in the medulla and pons. Some of these nuclei are binaural, receiving innervation from the cochlear nuclei on both sides, whereas others are innervated from the cochlear nucleus on only one side and are monaural. The outputs from all of these binaural and monaural nuclei then converge on the inferior colliculus (IC) in the midbrain [2–4]. The IC provides the principal source of innervation to the medial geniculate body [5,6] and, thus, indirectly to the auditory cortex (Fig. 1). Therefore, the IC is the nexus of the auditory system because it processes and integrates almost all ascending acoustic information from lower centers, and determines the form in which information is conveyed to higher regions in the forebrain.

Although the IC has been intensively studied, it remains an enigma. On the one hand, the response properties of IC neurons evoked by tones, noise or other conventional signals are, with only a few exceptions, very similar to the properties of neurons in one or another of the lower nuclei from which IC cells receive their innervation [7–12]. Such results were obtained in a variety of mammals, including echolocating bats. These similarities

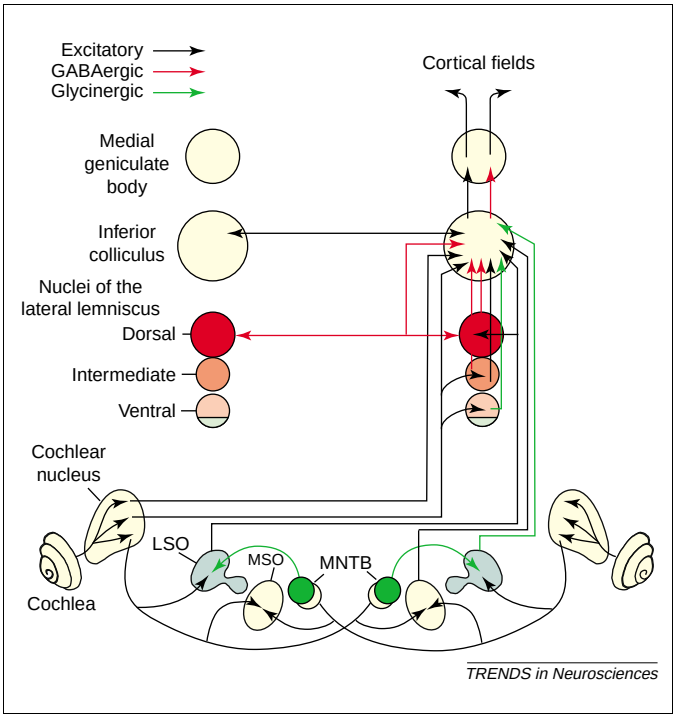

Fig. 1. Major connections of the ascending auditory system, showing the enormous convergence of projections onto the inferior colliculus from the majority of lower nuclei. Excitatory projections are shown as black lines and inhibitory projections are shown as red lines (GABAergic projections) or green lines (glycinergic projections). One of the parallel projections from the cochlear nucleus innervates the principal cell groups in the superior olivary complex: the medial nucleus of the trapezoid body (MNTB), and two binaural nuclei, the lateral superior olive (LSO) and the medial superior olive (MSO). The three principal nuclei of the lateral lemniscus (dorsal, ventral and intermediate) are situated rostral to the superior olive and just below the inferior colliculus. The ventral and intermediate nuclei receive innervation from only one ear and are, therefore, monaural; the dorsal nucleus of the lateral lemniscus receives innervation from both ears and is binaural. The dorsal nucleus is also GABAergic and provides strong inhibitory innervation to the inferior colliculus bilaterally and to the opposite dorsal nucleus via a commissural projection.

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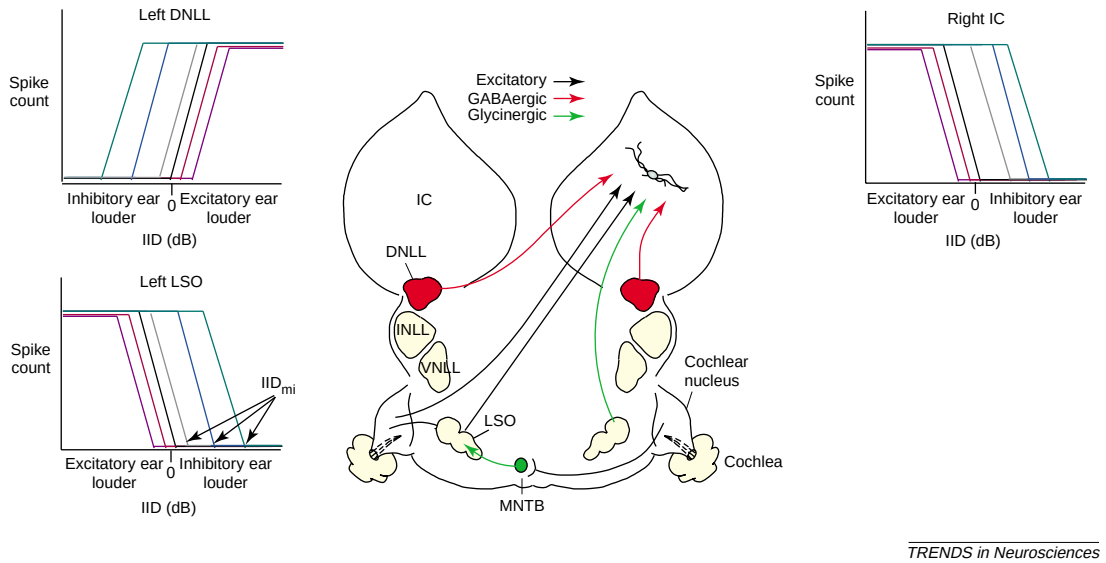

Fig. 2. The principal brainstem nuclei devoted to processing interaural intensity disparities (IIDs) are the lateral superior olive (LSO), the dorsal nucleus of the lateral lemniscus (DNLL) and the inferior colliculus (IC). The intensities received at the two ears are first processed binaurally in the LSO. The coded intensities are compared by subtraction, whereby the coded intensity from the ipsilateral ear excites each LSO neuron and the coded intensity from the contralateral ear inhibits each LSO neuron via glycinergic neurons from the medial nucleus of the trapezoid body (MNTB). EI properties (the ability to be excited by stimulation of one ear and inhibited by stimulation of the other ear) are studied by presenting a sound of fixed intensity to the excitatory ear to drive neuronal firing, and then documenting how progressively increasing sound intensity at the inhibitory ear reduces the discharges evoked by the sound at the excitatory ear. Because the excitatory intensity is fixed, each change in the inhibitory intensity generates a different IID. The IID function for each neuron plots these changes in spike count with IID, and the lowest IID that causes maximal suppression is the IID_{mi} of the neuron (arrows in plots of IIDs shown for the LSO). The IID functions of several LSO neurons are shown, to illustrate the range of IID_{mi} expressed by the LSO population. Virtually the same IID functions and range of IID_{mi} occur in the LSO, the DNLL ipsilateral to the excitatory input, and in the population of EI neurons in the IC contralateral to the excitatory input. The IID functions for the left DNLL are inverted versions of those of the left LSO and right IC because the DNLL on that side is inhibited by sound at the left ear and excited by sound at the right ear. Although the IID functions of IC cells are similar to those of LSO and DNLL cells, EI cells in the IC receive a large innervation from the LSO bilaterally, from the DNLL bilaterally, and from lower monaural nuclei, as illustrated by the projection from the cochlear nucleus. Abbreviations: INLL, intermediate nucleus of the lateral lemniscus; VNLL, ventral nucleus of the lateral lemniscus.

have led some investigators to the viewpoint that the major processing occurs in lower nuclei and that IC response properties are, for the most part, a reflection of the particular lower nuclei that innervate the IC cell in question [7–9]. On the other hand, substantial changes in most response properties occur when inhibitory inputs to the IC are blocked [12–20]. These results have led to an alternative viewpoint, which holds that the enormous convergence of excitatory and inhibitory inputs produces a corresponding degree of processing and, hence, substantial transformations of response features. As explained below, both viewpoints receive support from recent studies.

IC neurons and lower auditory nuclei often have similar response properties

Similar response properties in IC and lower nuclei are well illustrated by neurons that are excited by stimulation of one ear and inhibited by stimulation of the other ear (EI neurons). These neurons encode interaural intensity disparities (IIDs), the principal cues animals use to localize high frequency sounds [21]. EI properties are revealed by simply presenting a sound of fixed intensity to the excitatory ear and simultaneously presenting sounds of progressively increasing intensity to the opposite or inhibitory ear. The sound at the excitatory ear drives the neuron and this driven activity is progressively inhibited by increasing the intensity at the inhibitory ear. The feature we focus on is the smallest IID (the IID with the lowest intensity at the inhibitory ear) that evokes maximal spike suppression in each EI neuron, termed the IID of maximal inhibition (IID_{mi}) of the neuron (Fig. 2).

Neurons initially acquire EI properties in the lateral superior olive (LSO) [22–23] (Fig. 2). However, EI neurons are also prevalent in auditory nuclei above the LSO, especially in the dorsal nucleus of the lateral lemniscus (DNLL) [13,24–27], a purely GABAergic nucleus that projects bilaterally to the IC [25–29]. Additionally, EI cells dominate portions of the IC that receive innervation from the LSO and DNLL [3,30–35]. Because the LSO sends strong, excitatory projections to both the opposite DNLL and opposite IC (Fig. 1), it could be that the EI properties created in the LSO are simply imposed on their targets in the DNLL and IC. Indeed, many EI cells in the IC seem to be formed in this way [7,11,14,36], which supports the view that IC neurons reflect properties that were created in a lower nucleus, presumably the LSO (Fig. 3b).

EI neurons are formed in multiple ways in the IC

Subjecting IC neurons to more challenging tests, however, reveals that the EI properties of many IC cells are not simply a reflection of LSO projections. The first question these tests were designed to answer is simple: does the actual inhibition evoked by stimulation of the inhibitory ear occur in the IC or does it occur in a lower nucleus, presumably the LSO? If the inhibition occurs in the LSO, then blocking inhibition at the IC cell should have no effect on ipsilaterally evoked inhibition; the IC cell should be EI whether or not that inhibition is blocked at the IC (Fig. 3b).

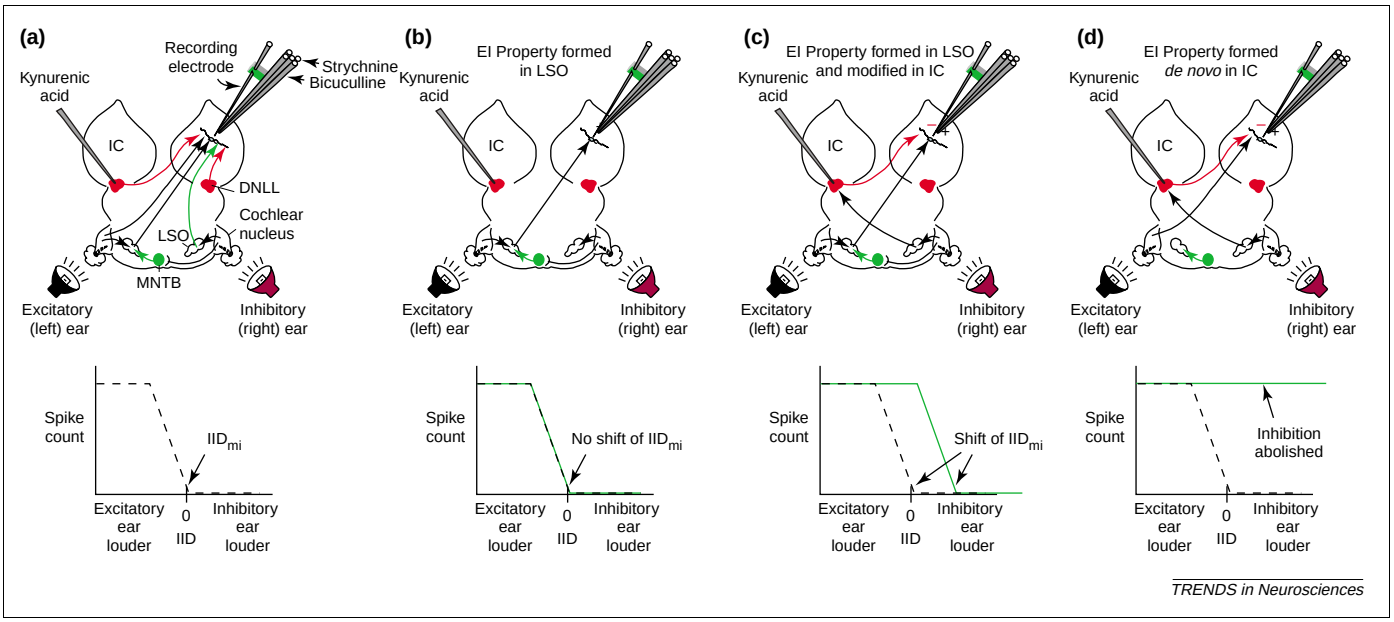

Fig. 3. Some principal connections from lower nuclei to EI neurons (neurons that are excited by stimulation of one ear and inhibited by stimulation of the other ear) in the inferior colliculus (IC) (a) and the various ways in which EI properties can be formed by subsets of those projections (b–d). The dorsal nucleus of the lateral lemniscus (DNLL, shown in red) is a purely GABAergic nucleus that provides strong inhibitory projections to both the ipsilateral and contralateral IC. Excitatory projections are shown as solid black lines and inhibitory projections as colored lines. The interaural intensity disparity (IID) function of an IC neuron is first evaluated by monitoring discharges in response to binaural stimulation using the recording barrel of a multi-barrel pipette (a). Bicuculline (an antagonist of $GABA_A$ receptors) or a combination of bicuculline and strychnine (an antagonist of glycine receptors) can be iontophoretically applied to an IC neuron, thereby blocking inhibition at the IC. Alternatively, the DNLL is reversibly inactivated by iontophoresis of kynurenic acid, a broad-spectrum blocker of glutamate receptors (b–d). IID function obtained before blocking inhibition is shown as dashed black lines and IID functions obtained after blocking inhibition are solid green lines. (b) Circuit showing how EI properties, which are first formed in the lateral superior olive (LSO), are imposed on the IC cell through a strong crossed excitatory projection. The IID functions of these IC cells are unchanged when inhibition is blocked at the IC or when the DNLL is reversibly inactivated. (c) Circuit showing how EI properties, which are first formed in the LSO, can be modified in the IC through the convergence of LSO and DNLL projections. The net effect of this convergence is to create EI cells in the IC that are suppressed by lower intensities at the ipsilateral ear than they would be if they received only the LSO projection (their IID_{mi} are shifted to the right when inhibition is blocked). The IID function obtained after blocking inhibition (solid green line) presumably reflects the IID function of the LSO projection. (d) Circuit showing how EI properties can be formed *de novo* in the IC. Stimulation of the ear contralateral to the IC (left ear) drives a lower monaural nucleus, shown generically here as the cochlear nucleus, which provides the excitation to the IC cell. Stimulation of the ear ipsilateral to the IC (right ear) excites the DNLL, which then provides the inhibition that suppresses the excitation in the IC evoked by stimulation of the left, excitatory ear. Blocking inhibition at the IC, or reversibly inactivating the DNLL with kynurenic acid, abolishes the inhibition evoked by the ipsilateral (right) ear and transforms what was previously a strongly inhibited EI cell into one that is monaural and influenced only by excitation evoked by stimulation of the left ear.

If, however, EI properties are completely or partially created in the IC through inhibitory projections from lower nuclei, then blocking inhibition at the IC should substantially reduce ipsilaterally evoked inhibition, or even abolish it completely (Fig. 3c,d). By evaluating the IC in this way, studies from several laboratories showed that the EI properties in the majority of IC cells are either modified or created *de novo* in the IC through a GABAergic inhibitory projection [12,19,37]. Moreover, by reversibly inactivating the opposite DNLL while recording from EI neurons in the IC, several studies in rats and bats showed that the source of the GABAergic inhibition is the contralateral DNLL [13,34,38]. As shown in Fig. 3, the effects of blocking inhibition are continuous, and range from no effect in some neurons, to shifts in the IID_{mi} (the most common modification of EI properties), to a complete or nearly complete elimination of inhibition – thereby transforming the neuron from one that was EI into a monaural neuron, which is only influenced by sound presented to one ear.

These data support the view that the IC is a center for integration and transformation but they also raise several questions. For example, why do the IID_{mi} of some IC cells have to be modified from circuit interactions? The populations of LSO and IC neurons express a similar range of IID_{mi}, [39–41] although the LSO population emphasizes IID_{mi} of ~0 dB, whereas the IC population emphasizes larger IID_{mi} (12–42). If the primary function of ipsilaterally evoked inhibition at the IC is to shift the IID_{mi} of some IC cells, it would seem more economical for the axons of LSO cells possessing the required IID_{mi} simply to branch more profusely to innervate a larger number of IC cells than LSO cells with other IID_{mi}. Such a differential innervation would create a population of IC cells that has the same range of IID_{mi} as the LSO population, but that would also have the expanded representation of larger IID_{mi} found in the EI population of the IC. An even more perplexing question is: what is the functional significance of recreating EI properties *de novo* in the IC when EI cells have already been created in abundance in the LSO? One insight into this question is provided by a unique feature of inhibition at the DNLL, as explained in the following section.

Properties of DNLL neurons predict emergent properties of some EI neurons in the IC

The DNLL, like the IC, receives a large complement of inputs from lower nuclei [32–45] and the neurons within it that are tuned to high frequencies are predominately, if not exclusively, EI [24,26,27,46]. Stimulation of the contralateral (excitatory) ear typically evokes a strong, sustained discharge train [13,47,48] (Fig. 4). The duration of the

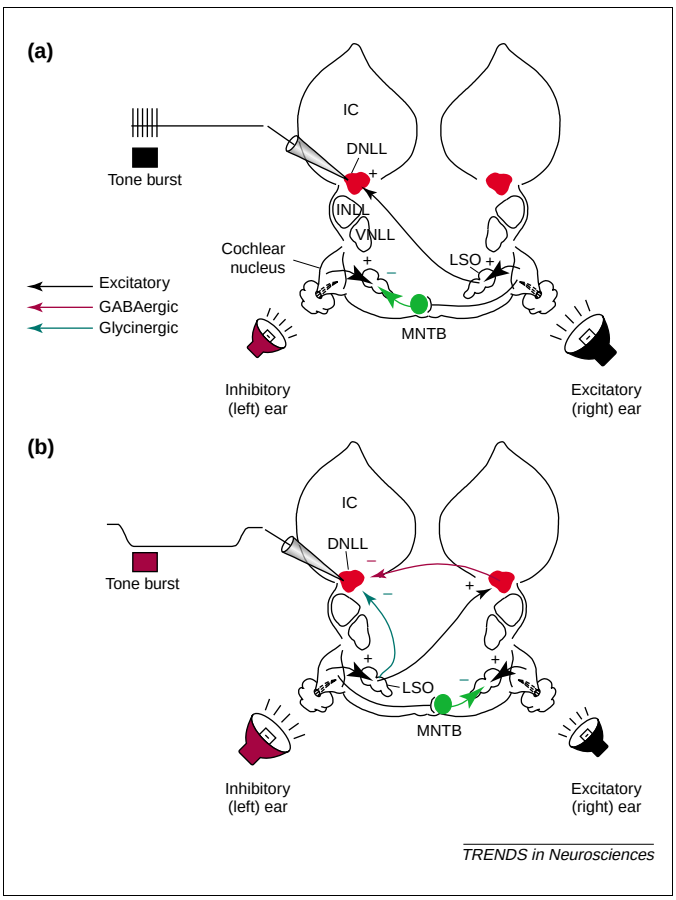

Fig. 4. Circuitry that creates EI properties (the ability to be excited by stimulation of one ear and inhibited by stimulation of the other ear) in neurons of the dorsal nucleus of the lateral lemniscus (DNLL). (a) Binaural signals that favor the contralateral (right) ear excite neurons in the lateral superior olive (LSO) that then excite DNLL neurons through a crossed excitatory projection. Each sound evokes a sustained discharge train in DNLL neurons with a duration equal to that of the stimulus (tone burst) duration. (b) Binaural signals that favor the ipsilateral (left) ear inhibit DNLL neurons. The inhibition is evoked through the LSO on the same (left) side. This LSO provides a strong glycinergic projection to the DNLL, but the same LSO excites the opposite DNLL. The opposite (right) DNLL sends a strong GABAergic projection through the commissure of Probst to inhibit the DNLL on the other (left) side. The noteworthy feature of the inhibition at the DNLL is that the resulting inhibition lasts substantially longer (on average ~18 ms longer) than the signal that generated it.

discharge train corresponds to the duration of the stimulus, and is never longer. By contrast, stimulation of the ipsilateral (inhibitory) ear evokes a long-lasting inhibition that persists for periods ranging 5–80 ms longer than the duration of the signals that generated it [13,27,49,50] (Fig. 4). The average duration of the persistent inhibition is ~18 ms. In other words, the DNLL remembers that a stimulus was received at the ipsilateral ear for ~18 ms, on average, after the stimulus has ended.

The persistent inhibition evoked by ipsilateral stimulation is potent and prevents DNLL neurons from responding to signals received at the excitatory (contralateral) ear for a period of time following the inhibitory signal [13,49,50]. Thus, the reception of an initial signal having an IID that favors the inhibitory ear functionally inactivates (persistently inhibits) the DNLL for a period of time. Because many IC cells derive their inhibition from the DNLL, during the period of persistent inhibition of the DNLL these IC cells are deprived of their inhibitory innervation and, thus, are temporarily transformed from strongly inhibited EI cells into weakly inhibited EI, or even monaural, cells [13].

These features suggest that the circuitry linking the DNLL with the IC is important for processing signals which generate IIDs that change over time, such as the IIDs that would be generated by moving stimuli or by multiple sound sources that emanate from different regions of space [12,13,49,51]. The rationale for this hypothesis is shown diagrammatically in Fig. 5. The hypothesis predicts that when two sounds with different IIDs are presented in close temporal sequence, there should be a change in the responsiveness of an IC cell to the trailing sound – a change produced by the reception of an earlier sound whose IID is strongly excitatory to the IC cell and inhibitory to the opposite DNLL (Fig. 5c). Stated differently, the reception of the first sound persistently inhibits the DNLL, thereby depriving the IC of its inhibitory input from the ipsilateral ear. Thus, when a trailing signal with an IID that would normally inhibit the IC cell is received, that signal excites the IC cell because the IC cell is deprived of its inhibitory input from the DNLL at that time. Conversely, the hypothesis also predicts that the responses to a trailing sound should be unchanged by an initial sound in IC neurons that are not innervated by the DNLL (Fig. 5d).

We tested and confirmed this hypothesis by presenting an initial and trailing sound while recording from IC cells in bats before and during reversible inactivation of the DNLL [12,13]. In many IC cells, the reception of an initial signal 'reconfigured the circuit' by persistently inhibiting the DNLL, thereby allowing the IC cell to respond to a trailing signal – a signal that inhibited the IC cell when presented by itself. In these cells, inactivating the DNLL by iontophoretic application of kynurenic acid (a broad spectrum blocker of glutamate-mediated transmission) relieved inhibition, and transformed that IC cell from one that was EI when the DNLL was functional into one that was monaural when the DNLL was inactivated. The reversible inactivation showed that the EI properties of these cells were created *de novo* in the IC, and that the DNLL provided the ipsilaterally evoked inhibition. In other IC cells, however, the initial signals had no effects on the responses evoked by the trailing signals; these cells responded to trailing signals as they did when the trailing signals were presented alone. Reversible inactivation of the DNLL had no influence on the EI properties of these cells, suggesting that the EI properties of these cells were formed in the LSO and imposed on their IC targets through an excitatory projection. Thus, the predictions of the hypothesis were confirmed both for IC cells that were innervated by the opposite DNLL and for EI cells that were not innervated by the opposite DNLL [13].

Functional relevance of emergent properties resulting from DNLL innervation

The demonstration that an initial signal can change the responsiveness of IC cells to a trailing signal suggests that the DNLL circuitry could contribute to a precedence-like effect [12,51]. The precedence effect, or law of the first wavefront, was discovered in human psychophysical studies and is due to a mechanism that suppresses the

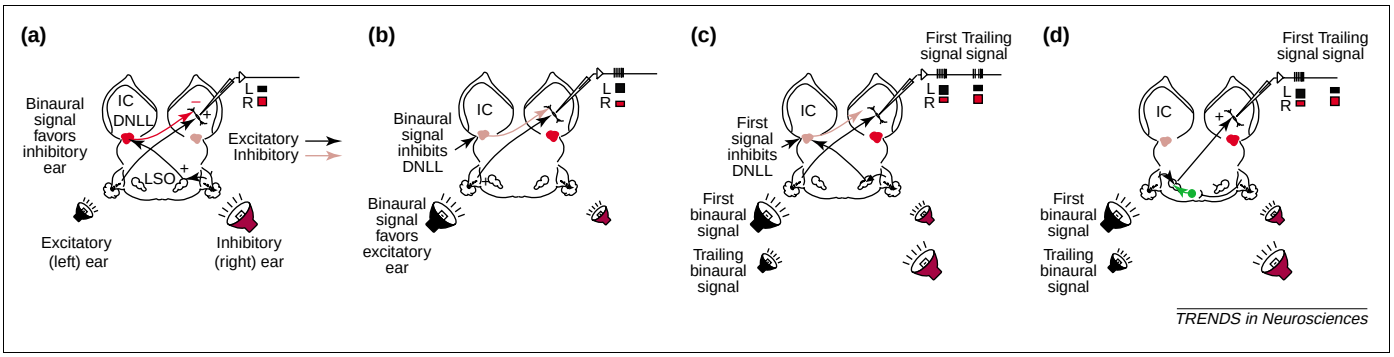

Fig. 5. How a binaural signal having an interaural intensity disparity (IID) that favors the ear contralateral to the inferior colliculus (IC) could reconfigure the circuit and, thus, allow the IC cell to respond to a trailing binaural signal to which it was unresponsive when the trailing signal was presented alone. (a) A binaural signal with an IID that favors the right ear (R), ipsilateral to the IC, drives two projections. The first is a GABAergic inhibitory projection from the opposite (left) dorsal nucleus of the lateral lemniscus (DNLL), which is strongly driven; the second an excitatory projection from a lower monaural nucleus (e.g. the cochlear nucleus), which is not as strongly driven. At this IID, the inhibitory projection from the left DNLL suppresses the excitation at the IC evoked by the weaker stimulation at the left (L), contralateral ear, so there is no overall response. (b) A binaural signal that favors the left, contralateral ear evokes a persistent inhibition in the DNLL (indicated by paler coloring), and the signal excites the right, contralateral IC. Inhibition at the DNLL is evoked by a glycinergic projection from the ipsilateral LSO and GABAergic inhibition from the opposite DNLL, as shown in Fig. 4. The excitation of the IC is through an excitatory projection from a lower monaural nucleus, shown here generically as coming from the cochlear nucleus. (c) The initial presentation of this binaural signal persistently inhibits the DNLL (indicated by paler coloring) but excites the IC, in the same way as shown in (b). When a trailing, binaural signal that favors the right (inhibitory) ear follows shortly thereafter, the IC neuron now responds to the trailing signal. The reason is that the first binaural signal generates persistent inhibition in the DNLL that deprives the IC cell of the inhibition that would be evoked by the trailing binaural signal if the trailing signal were presented alone. Thus, the weaker stimulus at the contralateral (left) ear evoked by the trailing signal is now free to drive the IC cell. (d) For IC neurons that are not innervated by the DNLL, initial signals do not change responses evoked by trailing signals. Whether the binaural signal is presented alone as in (a) or follows an initial signal as in (d), these neurons respond in virtually the same way to that binaural signal.

directional information carried by echoes. It explains how, in a reverberant room, a listener can localize only the first sound and not the sequence of echoes reflected from the various surfaces and objects in the room [52,53]. Precedence is classically demonstrated with two speakers, separated along the same plane in space [53]. The speakers emit identical sounds but the sound from one speaker is presented a few milliseconds before the sound from the other speaker. Listeners hear a single composite sound, and perceive the composite sound as originating from the leading speaker. The second sound fuses with the first and contributes to the overall volume and timbre of the fused sound, but is not perceived as a separate sound nor does it influence the perceived location of the composite sound. If the interval between the first and second sounds exceeds an upper limit, the two sounds are no longer heard as a single sound but as two separate sounds in succession, each with a perceived location in space.

It is noteworthy that precedence is a widespread, if not universal, feature of auditory systems. Precedence has been found in insects [54], birds [55] and a variety of mammals [52,53,56–59]. The effect is presumably a manifestation of mechanisms that could enhance the ability of an animal to focus on the primary or first sound in the midst of many sounds. Focus is achieved by localizing only the first sound and merging the percept of the first and trailing sounds, whereas sounds from other sources that are received after a certain interval would be resolved and localized.

The features of IC neurons produced by innervation from the DNLL described above could contribute to precedence [12,13]. The argument is that the IIDs generated by a sound from a particular location generate a population response in which some cells are excited while others are inhibited. Presumably this population response is interpreted by the brain as a sound that came from a unique location. However, a trailing sound that emanates from a different location would generate a distorted population response that cannot be associated with a location. The distorted population response is evoked by the trailing sound because many EI cells that should be inhibited by that sound are, instead, excited by the trailing sound, owing to the persistent inhibition at the DNLL produced by the initial sound.

Concluding comments

The circuitry linking the LSO, DNLL and IC can serve as a model for a more general understanding of how the integration of incoming information creates complex, but biologically meaningful, properties within the IC. Although the variety of response transformations that occur in the IC is far larger than described here for EI cells [12,20,60–65], we now have a better understanding of roles played by innervation from the DNLL for binaural processing. The significance of this is that it creates emergent properties in the IC, properties that are not possessed by LSO neurons or by IC cells that are not innervated by the DNLL. One property, but probably not the only one, is a change in the binaural responsiveness of the IC cell – a change produced by the reception of an earlier sound, the IID of which is strongly excitatory to the IC cell. Additionally, this emergent property occurs not only in *de novo* IC cells but also in all IC cells that have binaural properties shaped by projections from the DNLL.

Previously, we raised the question of why the shifts in IID_{mi} were constructed through circuit interactions rather than an exuberance of axonal branches from LSO cells with positive IID_{mi}. One dividend of constructing IC cells with inhibition from the DNLL, including those with shifted IID_{mi}, is that those cells would also express the emergent property described earlier in this review – a property they would not possess if their IID_{mi} were entirely imposed upon them from LSO projections or

were constructed from ipsilateral inhibitory projections from other sources.

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