Inhibitory circuits in sensory maps develop through excitation

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Inhibitory and excitatory connections are equal partners in determining neuronal response properties. Although the development and plasticity of excitatory networks have been heavily studied, little is known about how inhibitory circuits develop. In a recent study, Gunsoo Kim and Karl Kandler have shown that, as in the development of excitatory circuits, synapse elimination and strengthening are important processes for the development of well-organized inhibitory circuits.

The sensory world is mapped with great precision at many levels of the CNS. The response properties of the cells within these maps are derived from the interaction of excitatory and inhibitory inputs. Although understanding how the excitatory inputs develop their precise connections has been a significant focus of developmental neurobiology over the past 40 years, very little is known about how inhibitory circuits develop in the context of a sensory map. In their recent study [1], Kim and Kandler show that inhibitory circuits are refined by some of the same processes as excitatory circuits.

Refinement of maps in excitatory networks

Refinement of topographical maps has been observed in many excitatory networks. In the visual system, for example, developmental refinement is observed at several levels. Projections from the retina to the lateral geniculate nucleus are initially widespread and are subsequently trimmed down to a narrow strip within the correct eye lamina [2]. Similarly, projections from the lateral geniculate nucleus to the primary visual cortex are pruned from an initially exuberant arborization into eye-specific cortical columns [3].

In these excitatory networks, much of the refinement is due to activity-dependent plasticity. In the visual system, gradients of ephrins and Eph receptors contribute to the formation of the initial pattern of innervation [4] but activity in the retinae drives the refinement of eye maps in the lateral geniculate nucleus [5] and of retinotopic maps in the amphibian retinotectal system [6]. In the cortex, unequal visual activity in the two eyes can reorganize ocular-dominance columns during a developmental critical period [7,8]. Based on the development of these and similar excitatory networks, it seems that activity-dependent plasticity is a fundamental mechanism for their refinement.

An inhibitory circuit in the auditory brainstem

Within sensory systems, most inhibitory connections are local, arising from interneurons interspersed among excitatory neurons. As a result, it has been difficult to isolate inhibitory neurons or pathways to determine how their specific connections develop. Kim and Kandler took advantage of the rare sensory circuit in which inhibitory neurons and their axonal targets are well separated: the medial nucleus of the trapezoid body (MNTB) sends glycinergic inputs to the lateral superior olive (LSO) which, in the neonatal rat, is ~0.5 mm away (Fig. 1) [1]. This separation is large enough to allow stimulation at and recording from well-separated locations, but is small enough for both nuclei to be contained in a single brain slice.

The inhibitory projections between the MNTB and LSO are part of an auditory circuit that calculates the position of a sound source based on the difference in sound intensities at the two ears. An LSO neuron receives excitatory inputs from the ipsilateral side directly from the ventral cochlear nucleus, and inhibitory inputs from the contralateral side routed through the ipsilateral MNTB. Thus, a sound originating on the left side would excite the left LSO, but would inhibit the right LSO.

The LSO contains a detailed map of sound frequency (Fig. 1), in which both the excitatory and the inhibitory inputs are arranged according to their characteristic frequency. The localization of a sound source is performed

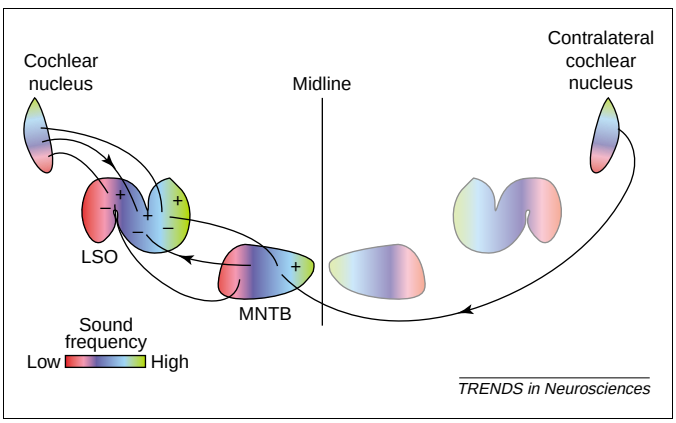

Fig. 1. The inhibitory circuitry of the superior olivary complex. A schematic of a coronal section through the rat auditory brain stem is shown. The lateral superior olive (LSO) calculates the location of a sound source in the ipsilateral auditory hemifield. It receives excitatory input from the ipsilateral cochlear nucleus, and inhibitory input from the contralateral side through the medial nucleus of the trapezoid body (MNTB). Sound frequency is mapped within each nucleus. Plus and minus symbols indicate excitatory and inhibitory connections, respectively.

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at each sound frequency. During development, therefore, both excitatory and inhibitory inputs must become restricted to the correct tonotopic position in the LSO [9]. By studying the pattern of projections from the MNTB to the LSO at different developmental stages, Kim and Kandler were able to show that the projection pattern is initially broad and is trimmed back over time.

Refinement of sensory maps in an inhibitory network

However, there is a problem with the idea of refining inhibitory networks through activity-dependent plasticity. Most synaptic learning rules follow a modified Hebb's rule [10], such that connections between neurons are strengthened if the firing of the presynaptic and postsynaptic neurons is correlated and are weakened if it is uncorrelated [11,12]. In contrast to an excitatory synapse, the firing of an inhibitory presynaptic neuron is necessarily anti-correlated with the firing of its postsynaptic partner. Based on the standard learning rules, therefore, it would seem impossible for inhibitory circuits to be refined through the strengthening of synapses.

Kim and Kandler's findings suggest, however, that the refinement of the MNTB–LSO inhibitory network results from both elimination and strengthening of synapses. Using a rat brain slice, Kim and Kandler recorded from individual LSO neurons using whole-cell patch clamp, while stimulating different locations within the MNTB through focal photo-uncaging of glutamate [13]. The region of the MNTB that projects to a single tonotopic location in the LSO was mapped out by systematically varying the location of glutamate release.

By mapping the pattern of inhibitory inputs to the rat LSO at different postnatal ages, it became clear that the development of these inhibitory connections follows the same pattern as the development of excitatory connections (Fig. 2). Initially [at postnatal day (P) 1], a large region of the MNTB projects to a given tonotopic location. By the time hearing starts (P11–P14), however, a much smaller region (~25% of the original size) of the MNTB projects to any given location within the LSO. During the first two weeks of life, therefore, functional synapses between the MNTB and LSO are pruned away to leave only connections that arise from a narrow range of auditory frequencies.

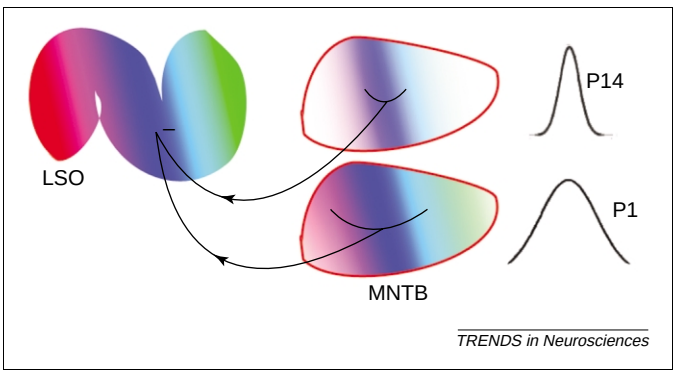

Fig. 2. The refinement of inputs from the medial nucleus of the trapezoid body (MNTB) to the lateral superior olive (LSO). Just after birth [postnatal day (P) 1], a large region of the MNTB projects to any given cell within the LSO. The distribution of MNTB neurons that project to a given cell in the LSO shrinks over the next two weeks. The colored regions in the MNTB represent the range of frequencies that projects to the specific location shown in the LSO.

At the same time that synapses are being pruned, the connections that remain become more effective. To demonstrate the increased effectiveness of individual fibers, MNTB fibers were electrically stimulated with a stimulus intensity low enough for postsynaptic responses to be observed only 30% of the time. At such low probabilities of a postsynaptic response, each postsynaptic response was almost certainly produced by the activity of only a single fiber. Using this procedure, Kim and Kandler found that stimulation of a single P14 MNTB fiber produced 12 times as much postsynaptic current as stimulation of a P1 fiber. Although it is not known whether the increase in current is due to stronger individual synapses or the presence of more synapses, the increased effectiveness suggests that strengthening synaptic connections within a restricted target is important in refining the inhibitory network.

Excitatory GABAergic and glycinergic synapses

Rather than relying on inhibitory interactions to drive the refinement of projections, the MNTB–LSO projections appear to be refined through excitatory glycinergic and GABAergic synapses. The time course of refinement follows the development of inhibition in the MNTB–LSO system. As is seen during the development of other inhibitory neurons [14], the Cl^- reversal potential in neurons of the LSO is relatively positive (−48 mV) at birth but becomes more negative (−82 mV) by the time of hearing onset [15]. During the refinement period, therefore, glycinergic and GABAergic inputs depolarize the postsynaptic cell [16], which can produce increases in postsynaptic Ca^{2+} concentration and can result in action potentials [17]. Only towards the end of the refinement period do the glycinergic inputs to the LSO actually inhibit its activity.

The correspondence between the time course of refinement and the development of inhibition supports a mechanism for refinement that relies on the excitatory properties of immature glycinergic and GABAergic synapses [18]. According to this proposed mechanism, spontaneous activity in the MNTB–LSO pathway drives postsynaptic activity during the refinement period. Similar to the manner in which current through NMDA channels mediates LTP and LTD, correlated presynaptic and postsynaptic activity would produce an increase in the postsynaptic Ca^{2+} concentration in the LSO neurons (as is suggested by the Ca^{2+} responses observed in Refs [17,18]). At locations where the postsynaptic activation is weak, as is likely at the edges of the broad innervation pattern in an immature LSO, synapses would be lost. Where the postsynaptic activation is strong, as is likely in the center of the innervation pattern in an immature map, synapses would be stabilized and added. At the end of the refinement period, a few days before the onset of hearing, the synapses become inhibitory, and this mechanism for synaptic plasticity is lost – leaving a well-ordered inhibitory map of the ipsilateral auditory hemifield.

The work of Kim and Kandler adds support to the hypothesis that plasticity at excitatory synapses sets the circuitry of the inhibitory tonotopic map in the LSO. Nonetheless, this evidence is only circumstantial.

Validation of the hypothesis awaits direct demonstration of activity-dependent plasticity at these immature synapses, of spontaneous activity in the circuit, and of disruption of normal map development when the excitatory GABAergic and glycinergic synapses are blocked. Just as the visual system has given us insight into the development of excitatory maps, the MNTB–LSO system is beginning to provide a wealth of information on the development of inhibitory maps.

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Making (a) sense of non-visual ocular photoreception

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A subset of intrinsically photosensitive retinal ganglion cells transduce information about ambient lighting conditions to areas of the brain involved in tasks including entrainment of the circadian clock, pupillary light reflexes and melatonin synthesis. The phototransduction system(s) utilized by these cells are unknown. Melanopsin and cryptochromes have been proposed as candidate photopigments for this system. Recent analyses of retinal degenerate mice lacking melanopsin or cryptochromes indicates that outer and inner photoreceptors can both contribute to non-visual photoresponses, and that both melanopsin and cryptochromes play important roles in this process.

The first definition for 'eye' in the Oxford English Dictionary is simply 'The organ of sight (in man and animals)'. But is this the sole function of the eye? Over the past decade, a second role for the eye has been uncovered: even in the absence of form vision, the eye can serve as a sensor for ambient lighting, akin to the light meter in a camera. A host of light-regulated functions, including entrainment of circadian clocks [1], suppression of activity by light [2], photic suppression of pineal melatonin synthesis [3], and pupillary light responses [4,5] are retained in mice that are blind as a result of mutations causing complete or near-complete degeneration of the classical photoreceptors, the rods and cones. These light-responsive functions are controlled by a retinal photoreceptor because mice lacking retinal ganglion cells lose circadian photoresponses, behavioral masking and pupillary light responses [6,7].

The discovery last year of intrinsically photoresponsive retinal ganglion cells (ipRGCs) has given non-visual phototransduction an anatomical basis [8]. Berson and colleagues used retrograde dye tracing from the circadian pacemaking cells in the rat suprachiasmatic nucleus to define direct retinohypothalamic-projecting ganglion cells; on patch-clamp recording, these cells were found to be

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