This Week in The Journal

Unexpected Heterogeneity in the Medial Superior Olive

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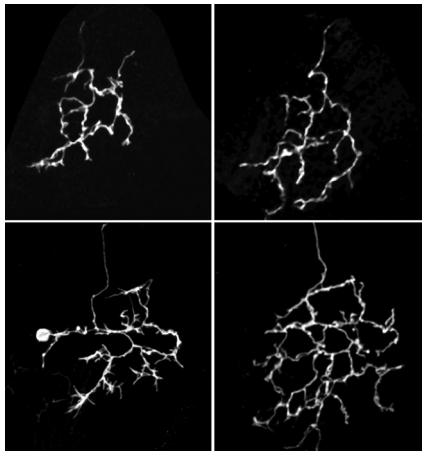
(see pages 6234–6245)

Birds and mammals can localize sounds in the horizontal plane by comparing the time of arrival of the sound at each ear. In mammals, interaural time differences are detected by neurons in the medial superior olive (MSO). Canonical neurons of the MSO have fast time constants, bipolar dendritic arbors, and phasic firing patterns. But some studies have suggested the MSO also has a second neuron type that has stellate morphology and regular spiking patterns. Little else is known about these neurons, except that they are not inhibitory interneurons. To characterize the neurons and distinguish them from canonical MSO neurons, Bondy, Haimes, et al. recorded from >400 neurons along the full extent of MSO in coronal brain slices from gerbils. Surprisingly, they found that MSO neurons have a range of physiological and morphological properties but cannot readily be divided into distinct groups.

Neurons in the center of the MSO had the classic properties of MSO neurons, with low input resistance and a fast membrane time constant; in response to step current injection, these neurons fired single spikes with single-phase afterhyperpolarizations. Such neurons were also present in dorsal and ventral MSO, but those regions also contained neurons that fired multiple spikes during depolarizing steps. In some of these neurons, an initial burst of spikes was followed by large, subthreshold membrane oscillations; in other neurons, spikes had two-phase afterhyperpolarizations. Some oscillator and tonic-spiking neurons had atypical morphologies. Nevertheless, all neurons received bilateral input from the cochlear nuclei and had similar axonal projections. Moreover, principal component analyses based on 12 physiological and 19 morphological parameters did not cluster neurons into discrete groups. Instead, the neurons appeared to form a single population exhibiting a spectrum of properties.

Injection of current to simulate input received during acoustic stimulation suggested that physiological heterogeneity allows MSO neurons to encode multiple types of information. Most notably, neurons that spiked multiple times during current steps could respond to input patterns characteristic of sounds with low-frequency amplitude modulation; canonical MSO neurons were unresponsive to such stimuli. These results suggest that the MSO has auditory functions beyond the detection of interaural time differences.



Zebrafish larvae exposed to lipopolysaccharide for 2 h at 3 dpf (bottom) have more complex retinal ganglion cell axons at 4 dpf (left) and 6 dpf (right) than untreated larvae (top). See Solek et al. for details.

Effects of Inflammation on Axon Development in Zebrafish

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(see pages 6353–6366)

Much evidence suggests that maternal infection during pregnancy can increase the risk of schizophrenia and autism spectrum disorders in offspring. The mechanisms underlying these effects are unclear. But many molecules classically associated with the immune system, including cytokines and components of the major histocompatibility complex and complement systems, are expressed normally in the developing nervous system and contribute to neurogenesis, migration, axon guidance, and synapse formation. These processes might be disrupted by changes in the balance of immune molecules during maternal infection.

To investigate how maternal infection might affect brain development, Solek et al. used zebrafish larvae. These larvae are transparent and develop outside the mother, allowing neuron growth to be monitored over time *in vivo*. To mimic inflammatory processes that may accompany maternal infection, larvae 3 d postfertilization (dpf) were placed for 2 h in media containing lipopolysaccharide. This induced an inflammatory response, as indicated by microglial activation and elevation of the cytokines interleukin-1β, interleukin-6, and tumor necrosis factor α. It also led to a rapid increase in the rate of axonal branch addition and retraction in retinal ganglion cell axons, which were just beginning to arborize in the optic tectum at 3 dpf. Notably, the brief exposure to lipopolysaccharide led to a persistent change in the axonal arbors of retinal ganglion cells: at 6 dpf, axons were longer and more elaborate in lipopolysaccharide-treated larvae than in controls. Perhaps as a result of this overgrowth, brightness discrimination and spatial acuity were impaired in lipopolysaccharide-treated fish. Knocking down interleukin-1β appeared to mimic the effects of lipopolysaccharide on axon growth and visually guided behavior, and it occluded the effect of lipopolysaccharide on these measures.

These results show that interleukin-1β is required for normal axon growth in zebrafish, as has previously been shown in rodents. More importantly, the results demonstrate that a transient inflammatory insult produces rapid effects on axon growth and branching, as well as persistent changes in axon arbor structure and behavior, in zebrafish larvae. Therefore, this model system may be useful for identifying the cellular and molecular mechanisms through which inflammation during brain development causes persistent behavioral effects.

This Week in The Journal was written by Teresa Esch, Ph.D.
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