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Timing Is Everything: Organization of Timing Circuits in Auditory and Electrical Sensory Systems

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Auditory and electrosensory systems are specialized to encode incoming sensory information, often with microsecond precision (Trussell, 2002). This kind of accurate coding is metabolically costly (Laughlin, 2001), but precise encoding of temporal information has direct behavioral relevance for sound localization and communication and appears to be the subject of selection. It is certainly true that the kinds of physiological and morphological adaptations that could improve temporal coding are found in the auditory brainstem of both birds and mammals and in the electrosensory system (Carr and Soares, 2002).

Why do the auditory and electrosensory systems go to so much expense to preserve temporal information? Most timing information is directed to the goal of accurately detecting time differences between two signals. Once the time difference is computed, the temporal code can be transformed into a new and less energetically expensive code of time or phase difference. Comparative studies of temporal coding in the auditory and electrosensory systems, including one from Matsushita and Kawasaki in this issue of the *Journal*, have identified circuits to detect time differences in all systems. All of these timing circuits share similar computational strategies and many morphological features.

In the auditory system, the secure and precise transmission of the phase-locked discharges of the auditory nerve fibers to their postsynaptic targets is mediated by the giant end-bulb synapse, which ensures fast, reliable, high-frequency excitatory transmission. Similarly shaped caliciform synapses are also present in higher order auditory neurons of mammalian time coding pathways, including neurons of the medial nucleus of the trapezoid body (Forsythe, 1994) and the type II neurons of the ventral nucleus of the lateral lemniscus (Wu, 2000) and in the chick ciliary ganglion (Paysan et al., 2000). In this issue, Matsushita and Kawasaki describe a new giant synapse in the electrosensory system of the weakly electric fish, *Gymnarchus*. The synapse originates from an electrosensory giant cell, which forms a socket-like structure around the cell body of an ovoidal cell. This study has two novel results. First, their discovery of a new nonfenestrated giant synapse raises the question of how such a synapse might function. Second, they describe a new circuit for detection of temporal disparity, leading to fresh insights into the functional organization of time coding circuits in auditory and electrosensory circuits.

HOW CAN GIANT SYNAPSES FUNCTION WITHOUT FENESTRATION?

Vertebrate giant synapses have been a favorite preparation for synaptic physiologists ever since it was discovered that they were large enough for whole cell recordings. The calyces and end bulbs of Held in the auditory brainstem joined the presynaptic terminal of the squid as a widely studied model system of neurotransmitter release (Forsythe, 1994). Whole-cell

recordings and improved imaging methods have resulted in a large amount of detailed data being collected from calyceal preparations, including the chick ciliary ganglion, chick auditory calyx (Sivaramakrishnan and Laurent, 1995), and the calyx of Held (Forsythe, 1994). Recordings from these large synapses have illuminated the mechanisms that underlie short-term synaptic plasticity (Von Gersdorff and Borst, 2002).

End bulbs form a fenestrated cup that envelopes most or part of the cell body and forms large numbers of active zones. The invasion of the presynaptic action potential into the calyx leads to the synchronous release of quanta at many sites, endowing this synapse with a high safety factor (Sabatini and Regehr, 1999). Studies of end bulbs in both the avian nucleus magnocellularis and the medial nucleus of the trapezoid body have shown that the invading presynaptic action potential is extremely narrow (Turecek and Trussell, 2001), probably due to rapid repolarization mediated by specific potassium conductances. Calcium influx into the presynaptic terminal is also brief and occurs only during the falling phase of the presynaptic action potential (Turecek and Trussell, 2001). Because the action potential is narrow, its downstroke occurs quickly, as does calcium influx, reducing the synaptic delay. The brief period of calcium influx produces a confined and phasic period of neurotransmitter release, increasing the temporal precision of transmission across the synapse (Brenowitz and Trussell, 2001).

End-bulb fenestrations provide sites at which rapid ion exchange can occur between extracellular spaces and the synaptic cleft, minimizing the kinds of calcium depletion in the cleft that can limit synaptic transmission (Nicol and Walmsley, 2002). There is also a strong dependence of end-bulb shape upon auditory experience and neural activity (Ryugo and Parks, 2003).

The morphology of the giant cell terminal in *Gymnarchus* is quite curious in light of the description above. It resembles other end bulbs in its large contact area with the postsynaptic membrane and numerous release sites. Nevertheless, it has none of the typical fenestrations observed in calyces or end bulbs. In fact, Matsushita and Kawasaki have shown that a single giant terminal can envelope several ovoidal cells. This finding raises several questions: How does current flow to produce giant cell-mediated excitatory postsynaptic currents? Where are the calcium channels needed for neurotransmitter release? What is the resistance of the truly extensive and uninterrupted synaptic cleft?

Matsushita and Kawasaki have shown that a single socket-like terminal covers approximately 84% of the soma of the postsynaptic cell, leaving little of the somatic membrane of the postsynaptic neuron exposed to free extracellular space. They point out that the continuous synaptic cleft over a large area around the soma must create a high-resistance path for current entering through postsynaptic receptors. This meets the conditions for producing an ephaptic effect of synaptic current on the presynaptic terminal, as originally suggested by Byzov for invaginating synapses between photoreceptors and their targets in the retina (see Kasyanov et al., 2000).

Byzov hypothesized that when the excitatory postsynaptic current depolarizes the postsynaptic membrane, it also creates a potential drop over the synaptic cleft resistance, which could depolarize the presynaptic membrane close to the locus of transmitter release. This may increase Ca^{2+} influx and transmitter release and create positive intrasynaptic feedback, thus acting as a retrograde signal. Matsushita and Kawasaki propose that ephaptic feedback could take place at the giant cell–ovoidal cell synapses of *Gymnarchus* due to the long and continuous synaptic cleft. The feedback would provide a mechanism whereby signals from large synapses would be amplified. The mechanism resembles the ephaptic

interaction at the Mauthner cell cap, except there the effect is inhibitory (Faber and Korn, 1989).

Would this mechanism increase the synchrony of transmitter release and increase temporal precision at this synapse? This remains to be seen. It is possible that yet another mechanisms for the modulation of transmitter release has evolved in this new synapse.

SIMILAR ALGORITHMS FOR DETECTION OF MICROSECOND TIME DIFFERENCES

Sensitivity to time disparities requires convergence of phase-locked signals from two different sources onto a time comparator. The existence of such a circuit was predicted for *Gymnarchus* (Kawasaki and Guo, 1996) and is described here by Matsushita and Kawasaki. The ovoidal cell in the electrosensory lateral line lobe receives phase-locked synaptic input from a giant cell onto its cell body and phase-locked synaptic input from a single S-afferent onto its dendrite. This convergence of temporal information satisfies the requirement for a comparator circuit and predicts that the ovoidal cell will be sensitive to phase differences between different parts of the body surface.

This circuit in *Gymnarchus* resembles a similar circuit in the unrelated South American weakly electric fish, *Eigenmannia* (Kawasaki, 1996). Both groups of weakly electric fish compare timing on the order of microseconds of sensory feedback from electric organ discharges received at different parts of its body surfaces. This capability is essential for and demonstrated by the jamming avoidance response (JAR). *Gymnarchus* and *Eigenmannia* exhibit a nearly identical JAR and share a rather complex but identical set of computational algorithms for computing the appropriate JAR (Kawasaki, 1997). Despite the algorithmic identity, Kawasaki and Guo (1996) showed that one of the computational steps, the timing comparison between body surfaces, occurs in the hindbrain in *Gymnarchus*, not in the midbrain as in *Eigenmannia*. Thus, similar systems with a similar overall function evolved differently in different genera by assigning the same task to different brain regions.

The phase difference detectors may be located in the midbrain in *Eigenmannia* and in the lateral line lobe in *Gymnarchus*, but the organization of the circuit is remarkably similar in both. In *Gymnarchus*, timing of the electric organ discharge on a small part of the body surface is encoded by phase locked action potentials in the S-type primary afferent fibers. Each afferent projects onto the dorsal dendrite of the ovoidal cell. The giant cells receive inputs from multiple S-afferents so are able provide global timing information for a large part of the body surface. Because giant cells form large end-bulb-like synapses on the cell body of ovoidal cells, the ovoidal cells can act as the time comparators to compare arrival times of action potentials from one giant cell terminal with input from one S-afferent terminal.

In *Eigenmannia*, the equivalent of the S-type afferents encode the timing of the electric organ discharge on a small part of the body surface. Each projects to a relay neuron that sends a projection to a dendrite of phase comparator cell (Carr, 1993). They also project to giant cells that form a large synapse on the cell body of the time comparator. Thus, the unrelated African and South American electric fish appear to have independently converged not only upon identical algorithms for encoding the timing of the stimulus, but also almost identical circuits for detecting timing differences between different parts of the body surface. In both cases, the fish receives a relayed timing signal onto its cell body and a direct timing signal onto its dendrite.

There is more to the story. The ovoidal cells contact the dendrite of pyramidal cells, which also receive S-afferent input. Pyramidal cells are also sensitive to phase differences and project to the midbrain. The details of the ovoidal cell to pyramidal cell circuit remain to be determined, but it seems likely that ovoidal cells detect phase differences and pass that sensitivity onto the pyramidal cells by means of a dendrodendritic gap junction connection.

Although both auditory and electrosensory systems encode timing information and detect differences in the microsecond range, the time difference detector works differently in each system. Timing difference detectors in birds and mammals are bitted neurons with inputs from each ear segregated onto two sets of dendrites (Carr et al., 2001). The neurons act as coincidence detectors and fire maximally when inputs from the ears coincide (or almost coincide). Why are timing difference detector neurons assembled differently in the auditory and electrosensory systems? It seems unlikely that the similarity comes from a similar structure in common ancestors, because the two groups of weakly electric fish independently derived their electric sense, and birds and mammals independently evolved the ability to hear airborne sound. It seems more likely that computational constraints instead directed selection. Perhaps electric fish need to compare a global electrical signal with a local one, while the auditory system compares two equal signals, one from each ear.

Matsushita and Kawasaki's study of a temporal difference detection circuit in the electrosensory system identifies computational strategies shared both with unrelated groups of electric fish, and with the auditory system of birds and mammals. The existence of parallel circuits allows us to identify shared algorithms and propose that these are suited to extracting the stimulus variables relevant for temporal coding.

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