Coincidence detection enhances appropriate wiring of the nervous system

Nicholas C. Spitzer*
Neurobiology Section and Center for Molecular Genetics, Division of Biological Sciences, University of California at San Diego, La Jolla, CA 92093-0357

Understanding how the spectacular complexity of connections among the neurons in the brain is established during embryonic development often is referred to as “the wiring problem.” Wiring assembly is viewed largely as a two-stage operation, involving axon pathfinding to reach the target and target selection that enables formation of appropriate synaptic connections (1, 2). The former entails growth cone migration that can occur over substantial distances and is considered to be driven largely by molecular cues; electrical activity is thought to play little role, with some exceptions (3, 4). The latter, involving sorting of axons in local regions, has been shown to involve electrical activity. Blocking action potentials with tetrodotoxin that plucks voltage-gated sodium channels leads to defects in the precision of synaptic connections (5). In a recent issue of PNAS, Kasyanov et al. (6) have tested the function of a different form of excitability in the establishment of functional connections in the hippocampus, a region of the brain known to be important for the formation of declarative memories. These new findings include identification of the function in the developing brain of a well described form of embryonic excitability, giant depolarizing potentials (GDPs; refs. 7 and 8), and illustrate a role for calcium signaling in synapse formation. The results also show that coincidence detection, long appreciated to play a role in strengthening synaptic connections in mature and developing nervous systems (9–11), can be important for establishing synaptic connections during embryogenesis.

Embryonic Forms of Excitability: The Phenomena and the Challenges

Electrical and chemical excitability have been studied extensively in the mature nervous system. The roles of voltage-gated ion channels in producing action potentials and the functions of neurotransmitter receptors in generating synaptic potentials are well established. Spontaneous activity has been appreciated to increase responsiveness to inputs because neurons are frequently close to threshold for action potential production, and information processing is enhanced by the opportunity to decrease as well as increase signal generation. The functions of action potentials, synaptic potentials, and spontaneous activity are far less understood in embryonic development and assembly of the nervous system. Excitability of the immature nervous system often entails calcium influx and release from calcium stores, separately or in combination; imaging with fluorescent reporters has revealed both transient and sustained elevations of intracellular calcium (12–22).

The Function of GDPs

GDPs have been studied in the postnatal rat hippocampus, but their functional role has been unclear. They are spontaneous, network-driven synaptic events generated by the neurotransmitter γ-aminobutyric acid (GABA), which is depolarizing and excitatory at early stages of development, and to a lesser extent by the excitatory transmitter glutamate. Depolarization stimulates calcium influx through N-methyl-D-aspartate (NMDA) receptors and voltage-gated calcium channels. GDPs are several hundreds of millisecond in duration, occur at frequencies of 0.05 to 0.5 Hz, and disappear shortly after birth when GABA becomes inhibitory. Their developmentally transient expression suggests that they have a function during this limited period. This is a plausible notion, given several lines of evidence suggesting that activity has functions in the formation of glutamatergic synapses. Synaptic inputs are often on dendritic spines, the morphology of which is activity-dependent. The density of NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors increases after blockade of activity. In the mature nervous system, long-term changes in synaptic efficacy can be achieved by pairing activation of pre- and postsynaptic neurons under conditions that lead to elevation of calcium ions in the postsynaptic cell (Fig. 1 A and B). However, initial morphological development of the brain is normal in Munc-18 knockout mice, which lack the ability to secrete neurotransmitter (23). Kasyanov et al. (6) have tested the hypothesis that the calcium signals generated by GDPs in rat CA3 pyramidal neurons alter synaptic transmission at immature synapses of mossy fiber axons onto CA3 neurons. Mossy fibers release GABA and glutamate, in contrast to inputs from interneurons releasing GABA alone, and these two inputs onto CA3 neurons can be distinguished by pharmacological and physiological parameters. Investigating this issue in...
hippocampal slices, in which GDPs are generated at the same frequency as in vivo (24), Kasyanov et al. find that pairing the rising phase of spontaneous GDPs with mossy fiber axon activation enhances the efficacy of the mossy fiber—CA3 synapse, assessed by several measures. The amplitudes of synaptic currents recorded before and after pairing are increased, and the incidence of failures of transmitter release is reduced for periods up to 30 min (Fig. 1C). This long-term potentiation (LTP) is associated with a decrease in the paired pulse ratio, the ratio of synaptic currents elicited in response to a pair of stimuli (S2/S1). This finding indicates an increase in the amount of releasable transmitter, because an increase in transmitter release in response to the first stimulus leads to a decrease in the amount released in response to the second stimulus. These changes are not observed in the absence of pairing of GDPs with mossy fiber stimulation. Of particular interest, presynaptically silent inputs, which yield no response to the first stimulus and occasional responses to the second, more reliably elicit responses after pairing.

Temporal and spatial specificity of this potentiation are also evident. The timing of pairing is shown to be critical; LTP declines to baseline when a delay of several seconds intervenes between GDPs and synaptic stimulation. GDP-induced potentiation is generally restricted to the paired mossy fiber input. These changes are also evident. The absence of pairing of GDPs with mossy fiber stimulation. Of particular interest, presynaptically silent inputs, which yield no response to the first stimulus and occasional responses to the second, more reliably elicit responses after pairing.

The results of Kasyanov et al. (6) raise further interesting questions. What is the molecular cascade by which the pairing of pre- and postsynaptic activity leads to changes in synaptic strength? Is it similar to those involved in spike-rate or spike timing-dependent LTP? Do increases in synaptic efficacy persist for periods longer than 30 min? The technical difficulties of recording for longer periods make this a challenging issue to address experimentally, but one may anticipate that the impact of the LTP is sustained. On this view, if GDPs were suppressed, one would expect the formation of mossy fiber–CA3 synapses to be disrupted. Targeted expression of inward rectifier potassium channels to hyperpolarize CA3 neurons and prevent activation of voltage-gated calcium channels in a CA3 NMDA receptor knock-out (28) could be useful in this regard. Are GDPs, or other forms of transient elevation of calcium in the postsynaptic target cell, a feature of formation of other synapses in the central nervous system? Do GDPs have other roles in neuronal differentiation in addition to synapse formation? GDPs have opened the door to further giant steps in understanding the roles of activity in assembly of the nervous system.

What Lies Ahead

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Coincidence Detection in Mature and Developing Nervous Systems

Coincidence of activity in presynaptic and postsynaptic neurons in the mature nervous system leads to changes in the strength of synaptic connections, as hypothesized by Hebb in 1949 (9). Coincidence detection in the mature nervous system has led to examination of this process in the immature nervous system, and the coincidence of firing of action potentials has been found to influence the formation and stabilization of synaptic connections during development. For example, induction of strabismus such that the eyes no longer have conjugate gaze leads to changes in ocular dominance assessed by the synaptic inputs to visual cortical neurons (25). Although the precision of timing is less refined, the coincident elevation of cyclic nucleotides in growth cones and their exposure to netrin-1 (26) yields turning responses distinct from those elicited to either agent alone. Similarly, fates of spinal cord neurons specified by combinatorial expression of transcription factors are distinct from those achieved by individual transcription factors (27). Coincidence detection provides a combinatorial code by which to achieve outcomes that cannot be generated by isolated stimuli and to increase the number of results attainable with a limited stimulus set.
