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Synaptic function and regulation

Editorial overview

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Introduction

Chemical synapses are the highly specialized intercellular connections that mediate information transmission in the nervous system. Their formidable capacity for plasticity is essential to proper wiring and maintenance of neural network and various computations performed by the brain. In turn, synaptic plasticity is integral to processes such as learning and memory, emotion, addiction and neurological disorders. Synaptic mechanisms are tackled at multiple levels – molecular, subcellular, cellular, small networks and behaviour – using a variety of experimental approaches. The last few years have witnessed remarkable progress at each of these levels of analysis, leading to new insights into the structure of synapses, the pathways that govern their formation and regulation, the contribution of synaptic properties to circuit function, and the relationship between synapse regulation and behavior.

This issue of Current Opinion of Neurobiology contains 21 articles highlighting recent advances in these different areas of synaptic research, and the breadth of topics emphasizes how this research impacts many other areas of neuroscience. Here we briefly discuss the key findings and their implications.

Synapse formation and maturation

Our understanding of how synaptic connections are formed has lagged behind that of how individual synapses function, as historically more efforts have been put into delineating the processes underlying neurotransmitter release and reception and their modulation. Nevertheless, with the identification of an increasing number of molecules supporting synapse formation and maturation, the last decade has seen a huge progress in this area. Notably for excitatory synapses, in addition to synapse adhesion proteins, a myriad of proteins that interact with glutamate receptors have been found to promote synapse maturation. Cadherins are one of the earliest molecules implicated in synapse formation. Extending the now well-established role of cadherin–catenin complexes in facilitating synaptogenesis and shaping dendritic spines, Brigidi and Bamji describe how signaling pathways involving cadherin and catenin regulators are integrated to the maintenance of structural connectivity. Amongst molecules that are important for inducing pre-synaptic and post-synaptic differentiation and maturation are secreted synaptic organizing proteins. Yuzaki reviews recent surprising findings on a cytokine family protein, Cbln1, which promotes synaptogenesis and is necessary for maintaining synaptic contacts in the adult cerebellum via formation of a tripartite complex with pre-synaptic and post-synaptic receptors. Focusing on the mechanisms of post-synaptic maturation, McMahon and Diaz review classes of synaptic organizing complexes that recruit glutamate receptors differentially. The three reviews underscore the

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emerging theme of cooperation or coordination between different adhesion systems in aspects of synaptogenesis and maintenance of synapse integrity.

Recent years have also witnessed an explosion of studies of synapses in brain areas classically studied at the circuit level, permitting an understanding of how synapse development and function impacts circuit-level refinement and processing. For example, although the lateral geniculate nucleus and development of its circuitry have been areas of intense focus for visual systems neuroscientists, our understanding of the molecular processes of synapse formation and refinement in this area has lagged. Hong and Chen describe the many phases of activity-dependent synapse refinement that occur in this brain area that likely contribute to the more classically studied circuit-level changes. Similarly, Oesch *et al.* demonstrate how characterization of synapses and cells within the retina has progressed to the point that an understanding is emerging of how the properties of each element in the retina sculpt the first stage of visual processing. Welie *et al.* bring similar analysis to developing cerebellar circuitry to understand how transient properties, like depolarizing GABA receptor mediated currents, contribute to post-natal circuit refinement. Lastly, Wilson exploits the recent functional analyses of Drosophila central synapses brought about by the introduction of whole-cell recordings to this preparation, to discuss how synaptic properties dictate the function of the antennal lobe.

Regulating pre-synaptic and post-synaptic organization and signaling

Early electron micrographs displaying pre-synaptic terminals that are full of synaptic vesicles have provided the unequivocal proof of the quantal nature of neurotransmitter release. Siksou *et al.* describe recent advances in electron microscopy that are revealing the pre-synaptic structure in unprecedented detail, providing insights into how distinct vesicle populations might be organized within the bouton. Fioravante and Regehr discuss our ever-growing understanding of the processes underlying rapid and activity-dependent regulation of the pre-synaptic terminal. While forming the foundation of quantal hypothesis, the nature of spontaneous release, particularly the extent to which spontaneous release shares the mechanisms of evoked release has remained enigmatic. Ramirez and Kavalali summarize the latest findings on this controversial topic.

Across the cleft, Mayer presents novel insights gained from the ultrastructure of glutamate receptors into the molecular steps underlying neurotransmitter detection. Downstream of glutamate receptor opening, post-synaptic signaling engages a variety of processes in which calcium plays a key function. Man highlights the importance of calcium-permeable AMPA receptors as signaling molecules that are integral to several forms of synaptic plasticity, and Bell and Hardingham review how synaptic activity, in particular, that which activates NMDA receptors, enhances pro-survival mechanisms to maintain neuronal health. Similarly, Xu discusses how the modular structure of PSD-95 acts to transduce the activation of NMDA receptors into the expression of the multiple forms of synaptic plasticity that are thought to underlie the rapid, activity-dependent regulation of hippocampal circuits. In an exciting recent development, Yasuda describes novel probes for use with fluorescence-lifetime imaging microscopy (FLIM) to monitor activation and compartmentalization of signaling molecules within stretches of active dendrites. This approach reveals that the properties of individual proteins, including CAMKII and small GTPases, directly determine the temporal and spatial scales of signal transduction within the dendrite.

Future studies directed at understanding how different receptor systems and subpopulations of receptors sharing the same post-synaptic compartment couple to particular signaling events, would be informative. This will be greatly assisted by developing integrated methods that allow individual synapses or dendrites to be analyzed at functional, biochemical and ultrastructural levels. In addition, a great deal more studies into the mechanisms of synaptic plasticity and modulation beyond excitatory synapses onto pyramidal and Purkinje cells is necessary to reveal the multitude of mechanisms of synapse regulation at play in the mammalian brain. These efforts are highlighted by the review of Lerner and Kreitzer on the mechanisms of synapse regulation in the striatum and the relationship of these processes to behavior. Similarly, Castillo *et al.* discuss the long-term, activity-dependent regulation of inhibitory synapses, and Chalifoux and Carter discuss how the activity of GABAergic synapses in turn, impacts the function of excitatory post-synaptic terminals via engagement of metabotropic receptors.

Signaling beyond excitatory pre-synaptic and post-synaptic terminals

Several reviews attempt to place synapses in a richer cellular and extracellular context by discussing how synaptic activity signals to distant organelles and how synapses fit into complex multicellular environments. Much of the pro-survival signaling, as emphasized in the Bell and Hardingham article, involves coordinate modulation of transcriptional programs by synaptic activity. The communication of distal signals back to the nucleus is important also during neuronal development, the induction of durable forms of synaptic plasticity, and axonal injury and regeneration. Ch'ng and Martin review recent advances in our understanding of molecular mechanisms of signaling back to the nucleus.

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Moving outside of the neuron synapses are surrounded by glial cells as well as by the extracellular matrix (ECM). Ditaytev and Rusakov discuss signaling involved in tetrapartite synaptic structures, highlighting the contribution of ECM molecules and glial processes in fine-tuning of different aspects of pre-synaptic and post-synaptic functions. Lastly, adult neurogenesis results in an ever-changing cellular environment. Inokuchi discusses exciting recent findings on how adult neurogenesis impacts learning and memory and how neural activity, in turn, modulates the extent of survival and integration of newborn neurons. This highlights the self-regulatory nature of network activity in rewiring itself, a detailed understanding of which would be synergistic to studies of the mechanisms of synapse formation and maintenance addressed earlier.

Summary

Our understanding of synapses has progressed tremendously and the processes underlying their formation and regulation are becoming increasingly clear. In addition, we are beginning to understand how the regulation of synapses on short and long-terms impacts circuit function and behavior. Nevertheless, a great deal remains to be uncovered and novel approaches are necessary both to push deeper into the inner workings of individual synapses and to integrate our new knowledge into models of emergent dynamic circuit properties. Furthermore, many classes of synapses and even many brain areas and organisms remain essentially unexplored, and vanguard research beyond these frontiers will undoubtedly continue to reveal unexpected mechanisms of neuronal communication.

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