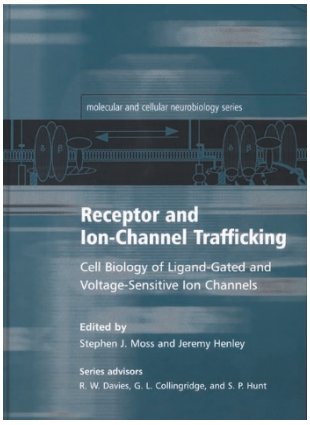
A walk on the wild side (of the synapse)



Receptor and Ion-Channel Trafficking: Cell biology of ligand-gated and voltage-sensitive ion channels
By Stephen J. Moss and Jeremy Henley
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Rapid information transfer between neurons occurs through the chemical synapse, where regulated exocytosis of neurotransmitter-containing synaptic vesicles from the pre-synaptic plasma membrane occurs in close proximity to specialized regions of the post-synaptic plasma membrane, where neurotransmitter receptors are concentrated. The presynaptic plasma membrane is a well known site of exocytic and endocytic membrane trafficking events, which are critical both for release of neurotransmitters and for subsequent retrieval and recycling of synaptic vesicle membrane components. By contrast, the post-synaptic plasma membrane has been viewed as a static structure, in which ion channels that function as receptors and transducers of the neurotransmitter signal are essentially fixed in place. This view has been dramatically overturned in the past several years. The post-synaptic side of the synapse is now recognized as a site of highly dynamic membrane trafficking events, where some neurotransmitter receptors shuttle between the plasma membrane and internal membrane structures within seconds or minutes, while other receptors present at the same synapse remain stably localized for hours or days. Moreover, these highly specific endocytic and exocytic post-synaptic trafficking events have been shown to be important in physiological processes ranging from neural development to synaptic plasticity. Moss and Henley chronicle this mini-revolution in *Receptor and Ion-Channel Trafficking*, which focuses on the cell biology of a number of ligand- and voltage-gated ion channels involved in post-synaptic neurotransmission. In doing so, they take us for an illuminating walk on an unexpectedly 'wild side' of the synapse.

Neurotransmitter receptors and ion channels tend to be complex, multi-subunit structures. In general, it is thought that subunit assembly occurs shortly after biosynthesis in the endoplasmic reticulum (ER) and that proper assembly of subunits is required for efficient ER export and subsequent anterograde trafficking to the plasma membrane. The book contains detailed discussions about the subunit composition of several types of ion channel. There is a section that summarizes the composition and membrane topology of distinct classes of potassium channels. Also discussed are emerging views about how subunit assembly is linked to ER export by assembly-dependent masking of a specific ER retention signal present in the cytoplasmic domain of channel subunits.

The post-synaptic plasma membrane is a highly organized structure, and one that has been characterized in great detail is the motor endplate of the neuromuscular synapse. Accordingly, considerable attention is given to the nicotinic acetyl choline receptor, a ligand-gated ion channel concentrated at the motor endplate. Evidence for a critical role of proper subunit assembly in producing functional post-synaptic receptors is summarized, and membrane trafficking events involved in localizing assembled receptors in the motor endplate during synapse development are discussed. Mechanisms that stabilize receptors at specific sites in the post-synaptic plasma membrane seem to be particularly important for the development of the motor endplate, and proposed roles of agrin signaling, dystrophins and the actin cytoskeleton are discussed.

Recent studies demonstrating rapid membrane trafficking of ionotropic glutamate receptors — the main ligand-gated ion channels mediating excitatory neurotransmission in the mammalian CNS — clearly demonstrate the highly dynamic nature of the post-synaptic membrane. Two major classes of ionotropic glutamate receptor are the so-called AMPA and NMDA receptors. These receptors colocalize in most excitatory synapses, but differ in key physiological properties. Membrane trafficking events dynamically regulate both the total number of glutamate receptors and the ratio of AMPA to NMDA receptors at individual synapses, thereby modulating synaptic plasticity underlying learning and memory. An authoritative review of AMPA receptor molecular biology and subunit composition is provided, key physiological evidence regarding roles of AMPA receptor trafficking in modulating synaptic plasticity are summarized, and evolving mechanistic models for how specific protein interactions regulate endocytic and exocytic membrane trafficking of AMPA receptors are discussed. Cell biologists may find it interesting to learn that the *N*-ethylmaleimide (NEM)-sensitive factor (NSF), a AAA-family ATPase that mediates SNARE complex disassembly, modulates AMPA receptor trafficking by a distinct mechanism involving direct binding to the receptor. A review of NMDA-type glutamate receptors is also provided, highlighting how a complex network of protein interactions involving specific PDZ domains modulates the insertion and stability of receptors in synaptic spines. Reviews of GABA (γ-amino butyric acid) and glycine receptors complete the biochemical perspective on the post-synaptic organization of ligand-gated ion channels.

Of course I have a few quibbles, most of which are minor and unavoidable in a book of this type. One can't cover everything, and certain topics (such as trafficking of ionotropic glutamate receptors) are moving so rapidly that it would be impossible to be fully up-to-date in any book. Overall, however, the editors and authors have done an excellent job of assembling a series of highly accessible snap-shots of an exciting and rapidly advancing area of cellular neurobiology.

Moss and Henley make a valuable contribution by highlighting major advances in the membrane trafficking of specific neurotransmitter receptors and ion channels, while revealing large areas in which additional cell biological investigation is sorely needed. For both reasons, this book is a most interesting and thought-provoking read. □

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