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Editorial

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A Molecular Window into the Brain: Special Issue on Molecules and the Brain

Unlocking the mysteries of the brain has long fascinated scientists and nonscientists alike. Fundamental questions of how memories are stored, of how the brain processes emotion, and of what constitutes consciousness continue to captivate and challenge neuroscientists. With the recent emergence of new technologies for studying and manipulating molecules, cells, and circuits, biological chemists have become increasingly empowered to explore the intricacies and complexities of the brain.

This special issue on Molecules and the Brain will explore the exciting field of molecular and chemical neuroscience. Research in this field strives to understand the brain at its most fundamental level through the study of molecules that underlie sensory perception, memory formation, neuroplasticity, and behavior. In this issue, we will consider the influence of molecules and structures spanning sizes ranging from single atoms to membrane receptors to the large protein-rich compartment known as the postsynaptic density.

A Viewpoint from *Stephen Lippard* (Massachusetts Institute of Technology, Cambridge, MA) highlights the discovery of a new role for mobile zinc in the brain. Release of synaptic zinc was found to regulate auditory processing in mice by tuning neurotransmission in response to loud sounds. These findings were made possible largely by non-invasive chemical agents that could rapidly intercept and selectively chelate zinc in freely moving animals. *Chris Chang* (University of California, Berkeley, Berkeley, CA) reviews a recent study demonstrating a nondeleterious role for reactive oxygen species-derived hydrogen peroxide (H_2O_2). A conditional lesion of the peripheral nervous system was found to recruit metalloprotein-derived H_2O_2 to a distal central nervous system lesion and promote axonal growth at this nonregenerative injury site. Together, these Viewpoints highlight the important signaling roles of metals, and the transient redox species they produce, in the nervous system.

Among the molecules central to learning and memory are ligand-gated ion channels, which are responsible for fast excitatory and inhibitory synaptic transmission. A collaborative effort between *Dennis Dougherty* (California Institute of Technology, Pasadena, CA) and *Sarah Lummis* (University of Cambridge, Cambridge, U.K.) explores the functional importance of conserved proline residues in the *Erwinia* ligand-gated ion channel, a bacterial homologue of vertebrate pentameric ligand-gated ion channels (pLGICs), using both natural and noncanonical amino acid mutagenesis. A companion paper from Sarah Lummis examines the roles of aromatic residues in the extracellular domain of the glycine receptor, an important member of the pLGIC family that mediates inhibitory neurotransmission and is linked to autism and other neurological disorders. Key aromatic residues that appear to be broadly conserved in Cys-loop receptors that contribute significantly to receptor activation were identified. Despite the information gleaned from recent high-resolution structures, understanding the precise mechanisms of channel gating and the interplay between different functional states remains a major challenge. These articles are excellent examples of the power of biochemical approaches to reveal new insights into the structure, dynamics, and mechanisms of ion channels.

Within the synapse, receptor channels are often concentrated at the postsynaptic membrane and embedded in a rich, dense protein network of scaffolding molecules, signaling enzymes, and cytoskeletal components, collectively known as the postsynaptic density. A Perspective from *Mary Kennedy* (California Institute of Technology) discusses key molecular aspects of this network and how it relates to synaptic plasticity. An exciting biochemical challenge for the future is to understand how this complex protein "machine" is assembled and dynamically regulated to increase or decrease the strength of synaptic transmission based on prior patterns of activity, a process believed to underlie learning and memory.

While the effects of fast-acting neurotransmitters, such as glutamate, occur within 1 ms via the opening of ion channels, the effects of biogenic amine and peptide neurotransmitters, as well as some effects of fast-acting neurotransmitters, are achieved over hundreds of milliseconds to minutes by slow synaptic transmission. This latter process is mediated by a complex sequence of biochemical steps involving secondary messengers, protein kinases, and other signaling proteins. A report from *Matthew Francis* and *Sanjay Kumar* (University of California, Berkeley) considers the impact of phosphorylation in the structural regulation of intrinsically disordered proteins (IDPs) such as neurofilaments. A potentially general strategy for engineering IDP-based interfaces is presented to probe the effects of multiple phosphorylation events on the conformation and electrostatic properties of surface-immobilized IDPs. In a Perspective by my group at the California Institute of Technology, we present an overview of chemical tools and technologies for studying a dynamic, inducible posttranslational modification in the brain known as O-GlcNAcylation. We discuss how quantitative, system-level approaches are a critical next step toward advancing a fundamental understanding of this modification in the brain, including its specific roles in neuronal signaling, learning and memory, and neurodegenerative diseases.

As the field of molecular neuroscience expands and attracts more biological chemists to ponder the seemingly endless mysteries of the brain, the hope is that new tools and technologies will be developed to drive major discoveries and conceptual breakthroughs. For example, *Charles Lieber* (Harvard University, Cambridge, MA) discusses the development of tissue-like mesh electronics, a new class of biomaterials that mimic the structural and mechanical properties of neural

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tissue and provide minimally invasive probes for monitoring brain activity. Moreover, as we continue to identify key molecular players, the next challenge will be to understand their dynamic interplay and explore ways to modulate their activity with the long-term goal of improving brain function or identifying novel targets and biomarkers for neurological diseases.

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