CHEMICAL REVIEWS

Editorial

Introduction: Chemical Approaches to Neurobiology

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Introduction: Chemical Approaches to Neurobiology

Dirk Trauner was born and grew up in Linz, Austria. After studying biology and then biochemistry at the University of Vienna, he joined Professor Johann Mulzer's group at the Free University of Berlin to pursue natural products synthesis. In the late 1990s, he was a postdoctoral fellow with Professor Samuel J. Danishefsky at the Memorial Sloan-Kettering Cancer Center in New York City. Subsequently, Dirk joined the University of California, Berkeley, where he currently resides as an associate professor of chemistry. In the summer of 2008, he will become a professor of Chemical Biology at the University of Munich. His research interests range from the biomimetic total synthesis of natural products to the development of neural receptors that respond to artificial input signals.

Neurobiology is one of the most rapidly advancing scientific fields of our time, and chemistry has done much to accelerate its progress. Indeed, as the molecular foundations of nervous systems become better known and new chemical tools become available, neurobiology is currently undergoing the same changes that propelled genetics to the forefront of science and led to the elucidation of the human genome. Chemistry plays a crucial role in this transformation, which may one day result in a true understanding of the most complex system known: the human brain.

Of course, chemists have made important contributions to the neurosciences for decades. Some major milestones include the discovery of selective channel blockers, the development of neuroleptic drugs, local anesthetics, calcium-sensitive dyes, or caged neurotransmitters. Indeed, small molecules have been indispensable for unraveling how neurons communicate and form neural networks. In recent years, however, their macromolecular receptors have become known in atomic detail as well. Perhaps as a result of this, the number of chemists and biochemists interested in the neurosciences has increased exponentially. Hence, a thematic issue of *Chemical Reviews* on "Chemical Approaches to Neurobiology" was simply overdue.

Neurobiology is a very large and rapidly expanding field and no single issue of a review journal could cover its depth entirely. To cope with this challenge, we have assembled a range of reviews that represent the diversity of the field and highlight the many ways in which chemical approaches can contribute to its advancement.

Molecular imaging, for instance, has already made a huge impact on the neurosciences, and several reviews in this issue center on this topic. Ametamey, Honer, and Schubiger provide a comprehensive overview of molecular imaging with positron emission tomography. Two other contributions deal with the imaging of metal ions in nervous systems using small molecule and protein probes: Que, Domaille, and Chang focus on the detection of zinc, iron, and copper, whereas the review of Mank and Griesbeck covers the development of genetically encoded calcium sensors. Choquet and colleagues give an overview of the various optical-based methods to monitor the dynamics of macromolecular complexes present at neuronal contacts.

Photochemistry, however, not only is employed to spy on neural systems but is equally useful for feeding information into them. Sjulson and Miesenböck comprehensively review the photocontrol of neuronal activity with various methods ranging from caged neurotransmitters to photoactuated ion channels. The emerging chemistry of caged calcium is laid out in a review by Ellis-Davies.

Several articles in this thematic issue are dedicated to structural and functional studies on the key protein players of neurobiology: Serotonin receptors, for instance, are reviewed by Nichols and Nichols. Dougherty makes a case that atomic structures alone are not sufficient to fully appreciate the functional sophistication of Cys-loop receptors, such as the famous nicotinic acetylcholine receptor. Transmembrane transporters, which play an equally important role in neural communication, are covered by Kanner and Zomot. The structure and regulation of SNARE proteins, which mediate the fusion of vesicles with cell membranes and neurotransmitter release, are reviewed by McNew.

In addition to "traditional" neurotransmitters or neuromodulators, several new classes of molecules have recently emerged that play crucial roles in the chemical signaling between neurons. Ahn, McKinney, and Cravatt discuss the fascinating chemistry and enzymatic regulation of lipophilic endocannabinoids. The emerging role of carbohydrates in neural signaling and development is comprehensively covered by Murrey and Hsieh-Wilson.

Three articles in this thematic issue deal with neuropharmacology. Prisinzano and Rothman review the diter-

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penoid salvinorin A and analogs thereof as probes in opioid pharmacology. In contrast to the vast majority of neurochemicals, salvinorin utterly lacks nitrogen. Wulff and Zhorov discuss potassium channel modulators for the treatment of neurological disorders and autoimmune diseases. In a review by Bauer and Stockwell on "neurochemical genetics", the usefulness of molecular libraries for the identification of neurobiologically active small molecules is demonstrated.

Therapeutical tools, however, are not confined to soluble small molecules alone. In addition, neural stem cells hold great promise for the remedy of neurological disorders. Little, Healy, and Schaffer show how chemical engineering can mediate the successful incorporation, survival, and integration of neural stem cells into the central nervous system

The 16 reviews by renowned experts in the field assembled in this thematic issue demonstrate how chemistry continues to make crucial contributions to the neurosciences. Since so much in this field remains unknown, opportunities abound to move into uncharted territory and the future of "chemical neurobiology" is very bright indeed. Close collaborations between chemists and neurobiologists have become common, and the academic boundaries between chemistry and neurobiology have begun to vanish. It is our hope that this issue of *Chemical Reviews* will be enjoyed by chemists and biologists alike and will stimulate some of our colleagues to consider new chemical approaches to neurobiology.

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