Sodium Channels, Pain, and Analgesia

Edited by *Kevin Coward* and *Mark D. Baker.*

Birkhäuser, Basel 2005. X + 199 pp., hardcover € 118.00.—ISBN 3-7643-7062-9

Chronic pain remains a major health problem, refractory to many treatments and likely to increase in those societies with a progressively aging population. Pain from disease, such as diabetes, from nerve injury (including, notably, several surgical procedures), and from persistent inflammation has been linked to hyperexcitability in the peripheral nervous system, a phenomenon strongly dependent on changes in ion channels in primary afferent neurons, most notably, in voltage-gated sodium channels. These facts set the background for the importance of this timely book.

In principle, if the sodium channel subtype that led to the hyperexcitability of nociceptors were known, it would be possible to design a selective inhibitor that would suppress the resultant hyperalgesia with, hopefully, little effect on other channels. This goal has been elusive, however, despite strong efforts over the past 10–15 years, at least in part because of our imperfect knowledge about which sodium channels are changed, whether they increase or decrease in expression, where in the neuron these changes occur, and in which neuronal types. This book considers many of these questions and points the reader in directions that might be helpful in addressing others.

The contents are useful as both review and future projection, and range from a description of the changes in the molecular phenotype of sodium channels caused by nerve injury, through the consideration of the roles of sodium channels in visceral and craniofacial pain, as well as the usually studied somatic pain, to a closing chapter that tersely considers emerging molecular biological and pharmacological aspects of sodium channels that might be exploited for analgesia in the future. Among the individual chapters, the overview of molecular changes in channel subtype expression in animals with somatic pain, from the Waxman laboratory, provides a broad overview and sets the ground for chapters on channel types contributing to visceral pain, by Laird and Cevero, and oral and craniofacial pain, by M. Gold. This latter work goes beyond the mere listing of sodium channel types to present a thoughtful treatise on the interactions of Na and K channels on overall excitability. Channels localized at nerve endings will have profound effects on transduction but are traditionally difficult to study, and these are thoughtfully analyzed by J. Brock, as is the basis for targeting the tetrodotoxin-resistant Nav1.8 channel, which is expressed exclusively in nociceptors (Dekker and Cronk). The chapters on accessory proteins for sodium channel functions, by Okuse and Baker, and on signaling cascades that modify sodium channel activities, by G. Nicol, are timely reviews of subjects that should be considered as important as channel expression for the control of excitability. The pharmacology of sodium channel inhibitors and its relationship to channel gating, which is the basis of the now classical "modulated receptor" model, fare well in the chapter by A. Scholz, but the chapter on current approaches to the discovery of sodium channel inhibitors for treating brain disorders is disappointing, not because of any special focus on the apparently unrelated field of brain disorders, but rather because the listed descriptions of methods were slimly tied to any mechanistic conclusions and pictures of computer simulations of the sodium channel with bound inhibitor were not connected to the changes in conformation that must accompany, and account for, the changes in inhibitor affinity.

Overall, this is a timely, well-written and useful text that is accessible to both the expert in ion channel research and the reader with a general neurobiological background.

Gary Strichartz
Harvard University (USA)
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Exploiting Chemical Diversity for Drug Discovery

Edited by *Paul A. Bartlett* and *Michael Entzeroth.*

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This book is almost as *diverse* as modern drug discovery itself, so don't let the title fool you: it is not a long treatise on the many ways to define and calculate the dis-similarity of molecules. Rather, the editors set out to "give readers a sense of the state of the art of drug discovery" in two of its main disciplines: chemistry and screening. This results in an original combination of topics.

The book starts with contemporary developments in synthetic chemistry. The first chapter gives a nicely exampled account of the value of polymer-supported reagents and scavengers in solution-phase synthesis and purification, while the second reviews the use of microwaves, ultrasound, and fluorous-phase techniques. Chapter 3 deals with biosynthetic routes to access polyketides not occurring naturally.

Compounds are the next main topic; chapter 4 outlines the different approaches available to combinatorial chemists for designing their libraries. How to manage the increasing numbers of compounds available from in-house synthesis and external providers is treated in the next chapter. This leads to the question how to measure *diversity* (frequently mentioned by chemists, but often only loosely defined) and use it in the design and selection process (chapter 6), while the subsequent chapter reflects on the current trend away from large, purely diversity-based libraries towards smaller ones with a focus on individual targets or target classes. The chemistry section closes with an article on the transformation of bioactive peptides into druglike small molecules.

The next section deals with technical aspects of high-throughput screening: chapter 9 examines the topic of plates and adapted liquid handling systems, followed by reviews on fluorescence-based detection techniques (chapter 10), cell-based assays (chapter 11) and advanced screening formats (chapter 13).

