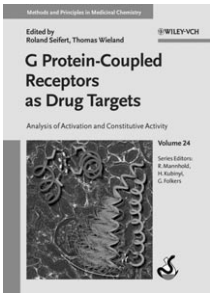
From Metal to Methyl

Methods and Principles in Medicinal Chemistry, Vol. 24: G Protein-Coupled Receptors as Drug Targets: Analysis of Activation and Constitutive Activity

Edited by *Roland Seifert* and *Thomas Weiland*.

Wiley-VCH, Weinheim 2005. xxv+279 pp., hardcover € 139.00.—ISBN 3-527-30819-9



In pharmacology, the definitions of agonist and antagonist are simple and incontrovertible, and both agonist and antagonist are indispensable in formulating the basic principles of drug action. Two decades ago, the idea of antagonists possessing the ability to elicit cellular responses other than by blocking the effects of agonists was viewed with skepticism, mainly because it contradicted the foundations of the receptor theory. Since Costa and Herz (1989) reported that ICI-174,864 (a δ-opioid antagonist) could reduce high-affinity GTP hydrolysis in NG108-15 neuroblastoma x glioma cell membranes, pharmacologists have come a long way in refining receptor theory to accommodate the notion of inverse agonists. The concept of the ligand-independent spontaneous activity of G protein-coupled receptors (GPCRs) has endured the test of time and is now generally accepted as the basis of inverse agonism, wherein antagonists can seemingly produce responses opposite to those elicited by agonists. "G Protein-Coupled Receptors as Drug Targets", edited by Roland Seifert and Thomas Wieland, represents a timely account of our current understanding of constitutively active GPCRs, a contemporary topic that is at the heart of receptor pharmacology. It is especially gratifying to note that each chapter is contributed by experts who are leading researchers in their fields.

The book has 15 chapters divided into two major sections: one deals with the concepts and models of constitutive receptor activity and the other provides in-depth analysis of selected GPCR systems. The book begins with a historical overview of the landmark discoveries that have shaped the concept of constitutive activity. Table 1.1 in Chapter 1 is particularly useful as a quick reference for over ninety different GPCRs that have been demonstrated to exhibit constitutive activity. The remainder of the first half of the book (Chapters 2–8) provides readers with detailed accounts of the molecular mechanisms of constitutive activity, cellular as well as physiological implications, and methods for analyzing constitutive GPCRs. For those who are into receptor pharmacology, Chapter 2 will be a delight to read. It describes the theoretical considerations of inverse agonism in a manner that is easy to follow; it is even possible to grasp the concept of the "Cubic Ternary Complex Model". The great strength of "G Protein-Coupled Receptors as Drug Targets" lies in its accurate portrayal of the importance of constitutively active GPCRs in drug design and development. In the past few years, we have witnessed the formation of biopharmaceutical companies with the aim of discovering novel inverse agonists through the creation and deployment of constitutively active GPCRs as tools for drug screening. A thorough understanding of how constitutive activity arises in wild-type, splice variants, and mutant GPCRs is very much sought after by researchers in both academia and industry. To this end, a catalogue of methodological approaches for studying constitutively active GPCRs (Chapter 8) allows one to reduce theory into practice. The reader can choose from a variety of in vitro and cellular assays to test for constitutive activity in GPCRs. Each approach is described in sufficient details for actual experimentation, and the authors have carefully considered the advantages and drawbacks of each method.

The second half of the book (Chapters 9–15) describes in detail the constitutive activity of a few selected GPCRs (α- and β-adrenergic, muscarinic, histaminergic, serotonergic, and chemokine receptors). Needless to say, comprehensive analysis is only given for the most widely studied constitutively active GPCRs amongst the ninety receptors listed in Table 1.1. The editors have done very well in selecting representative examples of constitutively active GPCRs. Surprisingly, the opioid receptors were not included in their selection. Given their historical relevance and therapeutic importance, one would have thought that the opioid receptors deserved a full account on their constitutive activity. It is also somewhat disappointing that the chapters (Chapters 9–15) on individual GPCRs invariably have a small section describing the molecular basis of constitutive activity, a topic that has been superbly and extensively covered in the first half of the book. It would have been much more enjoyable for the readers to just dive into the intricacies relating to each individual receptor rather than having to read through the basics again. Despite the minor redundancy in the introductory sections, the authors have effectively provided comprehensive, detailed, and up-to-date descriptions on each of the selected GPCRs. Such accounts represent valuable sources of information for researchers interested in those particular GPCRs. It is most fitting that the last chapter of the book deals with virally encoded constitutively active chemokine receptors. Clearly, nature has alluded to the importance of constitutive GPCR activity, and we need to devise strategy to combat viral

infection. Perhaps inverse agonists of chemokine receptors can eventually be employed as anti-viral drugs.

Everyone will be able to find their own favorite sections in this book. I especially appreciate the efforts made by the editors to include a chapter on linking constitutive GPCR activity to cell physiology and pathophysiology (Chapter 7). For those who are intrigued by the concept of inverse agonism, Chapter 7 provides convincing evidence that constitutive activity may play a special role in regulating our physiology, and that there is indeed therapeutic potential in the development of inverse agonists. Though not a novice in inverse agonism myself, I am indebted to the authors for introducing me to the wide variety of GPCRs that exhibit constitutive activity. The alarmingly large number of constitutively active GPCRs has profoundly changed my own thoughts on the biological significance of the various conformations of the GPCR. Overall, I find "G Protein-Coupled Receptors as Drug Targets" to be extremely informative and generally easy to read and understand. It is an important reference book for researchers (medicinal chemists, physiologists, and pharmacologists) working on the most favorite group of drug targets–the GPCRs.

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DNA Methylation: Approaches, Methods and Applications

Edited by *Manel Esteller.*

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The field of epigenetics and, more particularly DNA methylation, is constantly expanding, and most scientific disciplines are now concerned. The book *DNA Methylation: Approaches, Methods and Applications* presents an extensive overview of the role of DNA methylation in human physiology (genomic imprinting and X inactivation) and pathology (mostly cancer). It highlights the link between the biological role of DNA methylation in gene regulation and the pathogenesis of cancer. A few articles outline that a comprehensive analysis of epigenomes represents the next stage of biomarkers for detection and prognostic evaluation of cancer with subsequent outcomes in terms of treatment by demethylating agents, drugs acting on histone modification and possibly RNA interference against DNA methyltransferases.

The articles dedicated to the techniques of analysis of DNA methylation have been written by leaders in the field. They discuss the current approaches and protocols used to study DNA methylation and also other epigenetic modifications. The techniques are well described in terms of applications and protocols, and the benefits and caveats of each technique are particularly well addressed.

However, I think that the phenomenon of genomic imprinting deserved a full chapter (extension to other imprinting disorders, more illustrations, etc.) and also an emphasis of the imprinting risk of assisted reproductive technology.

It would have probably been easier for the reader to have the techniques of analysis of DNA methylation after bisulfite treatment (treated in two different chapters in the book) developed in only one chapter. The two chapters dedicated to the use of DNA demethylating agents are also sometimes redundant.

In conclusion, this book is interesting for both researchers and clinicians. It is an excellent summary of the subject for scientists starting in the field of epigenetics and it is also a reference book for professionals already familiar with the subject.

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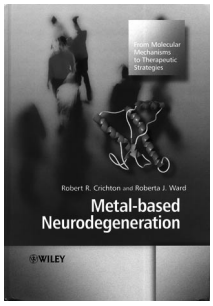
Metal-based Neurodegeneration: From Molecular Mechanisms to Therapeutic Strategies

By *Robert R. Crichton* and *Roberta J. Ward.*

Wiley, Chichester 2006. X+227 pp., hardcover £ 75.00.—ISBN 0-470-02255-8



Advances in health and medical treatments have resulted in dramatically increased life spans. However a consequence of this is that age-related neurodegenerative diseases such as Alzheimer's disease (AD) have become more prevalent. The escalating adverse social and economic costs associated with the increasing prevalence of these debilitating diseases means that effective therapeutic strategies are urgently required. Efficient design of therapeutic strategies requires intimate knowledge of the molecular pathways underlying these diseases.

Elucidating these molecular pathways is a very active area of research, and many different hypotheses have been put forward, among them metal-mediated oxidative stress. This book by Crichton and Ward gives an overview of the neurodegenerative diseases and how metal-mediated oxidative stress contributes to disease pathology. This book is extremely ambitious in scope as it not only attempts to cover the chemistry underpinning metal-mediated oxidative stress but also summarises what is known about a wide range of neurodegenerative diseases and the therapeutic strategies targeting them.

The first two chapters of the book deal with the chemistry and biochemistry of metal ions. In many ways these first two chapters are the most important and the best of the book as they deal with such fundamental processes as how metal ions are stored and transported. The links between tight regulation of metal homeostasis and the down-stream consequences this has for induction of

