The Receptors

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The Adenosine Receptors

Humana Press

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Foreword

It is an extraordinary pleasure to introduce the book *The Adenosine Receptors* edited by our friend and colleague Pier Andrea Borea, reporting the history, the pathophysiological roles, and the recent exciting developments of adenosine receptors.

Several decades have passed since purinergic signaling, i.e., the role of nucleotides and nucleosides as extracellular signaling molecules, was originally proposed by one of us (Burnstock G., "Purinergic nerves" *Pharmacological Reviews* 24: 509–581, 1972).

The concept of purinergic transmission was not, however, well accepted by the scientific community until the early 1990s, when evidence of the existence of receptor subtypes for purines and pyrimidines was brought forward by the cloning and characterization of four subtypes of the P1 (adenosine) receptors, seven subtypes of P2X ion channel receptors, and eight subtypes of the P2Y G protein-coupled receptors (Abbracchio M. & Burnstock G., "Nomenclature and classification of purinoceptors" *Pharmacological Reviews* 46:143–156, 1994). Early studies were largely concerned with the physiology, pharmacology, and biochemistry of purinergic signaling and demonstrated the role of adenosine 5′-triphosphate (ATP) (and its breakdown product adenosine) as a co-transmitter with classical transmitters in both the peripheral and central nervous systems. It was then showed that purines are powerful extracellular messengers also to non-neuronal cells, including secretory, exocrine and endocrine, endothelial, immune, musculoskeletal, and inflammatory cells. Purinergic signaling is rapid in neurotransmission, neuromodulation, and secretion, but it is also involved in long-term effects including proliferation, differentiation, migration, and death in development and regeneration.

As beautifully outlined in this very well-conceived and comprehensive book, we are now in the exciting phase when focus in the field primarily concerns the therapeutic potential linked to the pharmacological modulation of these receptors via selective agonists and antagonists.

The 24 chapters focus on the most updated and interesting developments related to the modulation of adenosine receptors in cardiovascular, neurodegenerative, inflammatory, and immune disorders.

We are sure that this work will contribute to diffuse the purinergic approach to the international scientific community and attract more young scientists to the field, to eventually solve the remaining issues related to the translation of basic purinergic research into the cure of human diseases, and possibly unveil further exciting applications.

Melbourne and Milan, April 2018
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Preface

I am pleased to be able to present this fascinating book, which details our current knowledge in the adenosine receptor (AR) field. Adenosine, a ubiquitously distributed endogenous nucleoside, is one of the major essential components of cellular life, and the 24 chapters in this book contain a wide range of up-to-date information, including various aspects of the biochemistry, molecular and cellular pharmacology, and physiology of adenosine and the G-protein-coupled receptors that it interacts with. These ARs, respectively named A_1, A_{2A}, A_{2B} and A_3, are distributed throughout the body and provide a means by which adenosine and its derivatives can modulate several normal and pathological processes, and the latest research into AR signal transduction pathways, new drug discoveries and potential therapeutic research are reported in depth. The chapters in this book cover both basic science, and preclinical and clinical applications, and thereby provide a scientifically excellent reference source.

The first chapter is dedicated to the status of art in adenosine and AR field. It spans the enormous amount of research carried out in the field worldwide since its discovery—which dates back to the early 1980s—and continues to yield new and surprising discoveries today. The vital role played by adenosine in various physiological functions is explored in Chap. 2, as well as the means by which its levels are kept in equilibrium by different enzymes and transporters. Indeed, components of extracellular adenosine homeostasis are implicated in various pathological conditions.

Chapter 3 goes on to analyse the widespread distribution and signalling events of the ARs, together with their molecular structure and signal transduction pathways. Chapters 4, 5, 6, 7 focus on a detailed chemical analysis of the selective agonists, antagonists, partial agonists and allosteric modulators of A_1, A_{2A}, A_{2B} and A_3ARs, in addition to the structure-activity relationships (SARs) of the compounds interacting with ARs. The potential applications of these compounds as both pharmacological tools and therapeutic agents are discussed.

Investigations into the thermodynamic parameters of the compounds interacting with ARs are detailed in Chap. 8. Intriguingly, findings to date suggest that the binding of AR agonists may be entropy-driven, while AR antagonist binding may be enthalpy-driven—a phenomenon known as thermodynamic discrimination.

Adenosine tone and ARs are involved in a number of processes critical for neuronal functions and homeostasis. These include the modulation of synaptic activity and excitotoxicity, the control of neurotrophin levels and functions, and the regulation of protein degradation mechanisms. As reported in the following chapters, ARs play a range of roles in neuroinflammation (Chap. 9); Parkinson's, Alzheimer's and Huntington's diseases (Chaps. 10, 11 and 12); epileptic seizures and in brain ischemia (Chaps. 13 and 14, respectively); as well as the control of cognition and pain (Chaps. 15 and 16). New pathophysiological insights and recent research developments regarding purinergic signalling in the cardiovascular system have opened new therapeutic avenues for the treatment of the infarcted heart (Chap. 17). Moreover, numerous studies indicate that adenosine signal transduction is involved in asthma and chronic obstructive pulmonary diseases (Chap. 18), as well as in renal failure (Chap. 19).

In fact, the engagement of ARs on the surface of several immune cell populations—including neutrophils, macrophages, dendritic cells, mast cells and lymphocytes—shapes a broad array of immune cell functions, which include cytokine production, degranulation, chemotaxis, cytotoxicity, apoptosis and proliferation (Chap. 20). The critical role of adenosine in maintaining cartilage and chondrocyte homeostasis under physiological conditions—and its selective protection against the onset of osteoarthritis—is described (Chap. 21). Interestingly, AR agonists and/or antagonists may also conceivably be employed in the fight against diabetes mellitus and obesity, as they act to normalise lipolysis, insulin sensitivity and thermogenesis (Chap. 22).

Regarding ARs' anticancer applications, Chap. 23 reports how A_{2A}AR antagonists may enhance tumour immunotherapy in cancer treatment protocols. Indeed, the effectiveness of A_3AR agonists in several animal tumour models has already led to preclinical and clinical trials of these molecules. Furthermore, the relevance and action of ARs and pulsed electromagnetic fields (PEMFs) are explored in various inflammatory diseases of both the peripheral and central nervous system; in this context it appears that PEMFs may be a useful, non-invasive anti-inflammatory treatment with only minor impact on daily life (Chap. 24).

I thank all the scientists and young investigators who have made contributions to this book, furthering the status of the art in AR research. I trust that their remarkable achievements are sufficient to highlight the potential of ARs in many health and disease contexts. If one overarching conclusion can be drawn from this book, it is that engagement of the scientific community in multidisciplinary AR research projects will almost certainly lead to discoveries that will translate into the development of better targeted and more efficacious treatments; novel adenosine drugs will undoubtedly have fundamental roles to play in both safeguarding and improving human health.

Last, but certainly not least, I thank the members of my Research Group for their scientific work in the field of adenosine receptors, and Dr. William F. Curtis (Executive Vice-President), Dr. Giuseppe di Giovanni (Series Editor), and Dr. Jayashree Dhakshnamoorthy and Dr. Simina Calin (Neuroscience Editors) at Springer International Publishing.

Ferrara, Italy Pier Andrea Borea

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