

Preface

This book is an enthusiastic celebration of cyclic guanosine monophosphate (cGMP) and amply illustrates the importance of this field of science to patients and how it has evolved. Cyclic GMP, until recently the forgotten sibling of cyclic adenosine monophosphate (cAMP), was discovered as a second messenger in the late 1960s. For many years, cGMP retained the status of a sleeping princess. Indeed, the biological role of cGMP was unknown until the 1980s, when two key discoveries were made. First, it was found that natriuretic peptides (NP) could stimulate cGMP synthesis by binding to the particulate guanylate cyclase (pGC). Second, it became apparent that nitrovasodilators such as glycerol trinitrate, which liberate nitric oxide (NO), are potent activators of the cGMP-forming signaling enzyme, soluble guanylate cyclase (sGC). After the discovery of endogenous NO formation in the late 1980s and the 1998 Nobel Prize in Physiology or Medicine, many researchers and physicians again became interested in the NO/sGC interaction and cGMP-dependent signaling.

Cyclic GMP plays a key role in the regulation of cardiovascular homeostasis including smooth muscle relaxation, platelet inhibition and vascular growth and differentiation, and we are beginning to understand the respective molecular mechanisms downstream of cGMP. Subsequently, the effector systems of cGMP - protein kinases, ion channels and phosphodiesterases - have emerged as sub-fields of cGMP research and therapeutic targets. Since this complexity of cGMP formation, metabolism and effectors now underscore the importance of cGMP signaling, it is time to integrate all aspects of cGMP for the first time in one book, about half a century after its discovery.

This book is exclusively devoted to this exciting and important signaling molecule, addressing all recent advances in understanding guanylate cyclase regulation, NO/sGC interactions, cGMP effector mechanisms and their pathophysiological and pharmacological implications. Particular attention will also be given to clinical applications of the novel cGMP-elevating drugs which are on the horizon, thus spanning the continuum from basic science to clinic.

The first part of the book deals with the basic generators and effectors of cGMP. The middle section explores how pharmacologically active compounds can expand

our understanding of physiology and pathophysiology. The concluding section surveys the relevance of cGMP to disease, and therapeutic applications of novel cGMP-elevating compounds.

There is tremendous promise behind cGMP itself, as well as the numerous other molecules and processes associated with the NO/sGC/cGMP and NP/pGC/cGMP pathways. Collaborative efforts among biochemists, physiologists, pharmacologists and clinicians are the key in realizing this promise. Undoubtedly, exciting times lie ahead for the GC field.

If this book helps to boost further the rapidly evolving cGMP field, which is now undergoing a transition from basic science to clinical applications, to improve care and treatment of patients, the efforts of the editors and our editorial assistant Susanne Dathe will not have been in vain.

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cGMP: Generators, Effectors and Therapeutic
Implications

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