
Preface

In general, the purpose of the series *Handbook of Experimental Pharmacology* is to critically review and summarize the state-of-the-art of a well-established scientific field. For this volume, this situation is quite different: Here, experts from various disciplines discuss a young field. The development of the area was impeded by previous methodological difficulties that have been overcome only recently. Accordingly, the book also discusses scientific gaps in our knowledge and aims to foster further research. I am thankful to the Editors of the *Handbook of Experimental Pharmacology* for giving me the opportunity to put together this book.

The book is about cyclic nucleotides (cNMPs). cAMP and cGMP are firmly established second messenger molecules with broad pharmacotherapeutic implications. These two cNMPs are also designated as *canonical cNMPs*. cAMP and cGMP have several relatives that are designated as *noncanonical cNMPs*. A major focus of this book is to discuss the cyclic pyrimidine nucleotides cCMP and cUMP with respect to their endogenous and bacterial generators, effectors, biological functions, and elimination. The chapters cover both conceptual and methodological aspects. Most importantly, the recent development of the field was strongly enhanced by new analytical methods for cNMP detection and the synthesis of cNMP analogs that can be used as experimental tools.

In addition to cCMP and cUMP, this book covers cNMPs related to cGMP, i.e., cIMP, 8-nitro-cGMP, and the cyclic dinucleotide cGAMP. Hence, this volume is a logical continuation of Volume 191 of the *Handbook of Experimental Pharmacology* (2009) edited by H.H. Schmidt, F. Hofmann, and J.P. Stasch, entitled *cGMP: Generators, Effectors and Therapeutic Implications*. Lastly, the present volume covers 2',3'-cNMPs. The major difference between 2',3'-cNMPs and the cNMPs mentioned above (cAMP, cGMP, cCMP, cUMP, cIMP, and 8-nitro-cGMP) is the nature of the phosphodiester bond (3',5' in the latter compounds). However, this apparently small chemical difference has major consequences for biological effects.

As is expected from a young field, currently, there is not yet an established pharmacotherapeutic application. More systematic basic research in multiple biological systems is required. Nonetheless, it is beginning to emerge that each cNMP plays a unique functional role that could be exploited therapeutically. One particularly prominent case is the cUMP generated by *Pseudomonas aeruginosa*

toxin ExoY. Targeting cUMP may be an approach to treat infection with this Gram-negative bacterium, a major problem in hospitalized patients and patients with cystic fibrosis.

I am very indebted to all the authors who prepared their chapters so carefully and implemented all my suggestions for revision. All authors of this book have made substantial experimental, methodological, and/or conceptual contributions to the field and present personal but balanced views on specific aspects.

I also would like to thank the editorial team from Springer for their dedication to complete publication of the book.

As with many multiauthor books, it took more time to complete all chapters than originally planned, a major reason being that several authors wished to include very recently published peer-reviewed data into their chapters. After completion of several chapters, some new and important findings were published. Specifically, the natural compound thymoquinone was identified as a pharmacological tool to manipulate cIMP levels [Detremmerie et al. (2016) *J Pharmacol Exp Ther* 358:558]. Moreover, crystal structures of HCN channel 2 in complex with noncanonical cNMPs have been resolved [Ng et al. (2016) *Structure* 24:1629]. These data highlight that even in a small field, scientific progress can be so fast that it is difficult for a multiauthor book to be at the cutting edge.

I hope that this book offers a suitable platform for both cNMP aficionados and newcomers to conduct productive research in this exciting area. If the field develops, perhaps, in 20 years, another volume on the topic is warranted in the *Handbook of Experimental Pharmacology*.

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