

Book Review

Endothelin: Molecular Biology, Physiology, and Pathology

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Ten years after the structure of endothelin-1 was first reported in *Nature*, this book describes the progress to date in defining the physiological and pathological significance of this molecule. In many respects, this field has been remarkable for the speed with which the resources of the pharmaceutical industry have been applied to the development of a range of high-affinity receptor antagonists. Whether some of these become the medicines of the future is something that scientists, clinicians and pharmaceutical company executives await with considerable anticipation.

For those unfamiliar with the endothelins, this is a useful volume as there are some good reviews of the areas covered. It should therefore be included in libraries of schools of medicine, pharmacy, and pharmacology. However, this is not the definitive text the cover suggests it might be. There is no detailed account of the factors inducing endothelin synthesis, and which provide further indicators as to the physiological and pathological roles of endothelin. The field of endothelin-converting enzyme is still the subject of some misunderstanding and controversy, and this is not fully explained. But perhaps most importantly, until clinical trial data has been published and the therapeutic usefulness of endothelin antagonists established, it is difficult to write a fully comprehensive account of the success of ten years of research in this field. Nevertheless, those unfamiliar with the achievements in this field who would like to have an insight into the extensive scientific literature on endothelin, will do well to read this book.

Every aspect of research in this field has been underpinned by modern techniques in combination with more traditional methods. Chapters 1, 2, 6, 7 and 8 provide a detailed picture of endothelin pharmacology and the various steps in the rapid development of specific endothelin antagonists. This includes the characterization of endothelin receptor subtypes, the application of molecular biology to structure-activity relationships and antagonist interactions with endothelin receptors, the design of potent antagonists, and the use of

these agents to demonstrate potential roles for endothelin in animal models of disease. Indeed, to some extent, this book is a self-contained course in experimental pharmacology.

The fascinating subject of endothelin-converting enzyme is covered relatively briefly in chapter 3. The endothelins are synthesized as inactive precursors dependent on an unusual enzymatic cleavage to generate the active vasoconstrictor. The peptidase involved is widely referred to as endothelin-converting enzyme (ECE), and represents a therapeutic target of equal or greater importance to that of endothelin receptors. However, it has proved far from easy to identify the physiologically relevant ECE. This chapter provides a reasonable account of the work to date, but fails to critically evaluate the endeavours, not least, the proof that the purified and cloned peptidase called ECE-1 plays a role in the endogenous biosynthesis of endothelin. ECE-1 gene knockout results in a phenotype similar to endothelin-1 gene knockout, but the biochemical evidence does not fully support the hypothesis that this similarity is due to interference with endothelin synthesis. Unfortunately, no selective inhibitors are as yet available for testing the role of ECE-1 in endogenous endothelin synthesis.

Chapters 4 and 5 provide excellent reviews of endothelin signal transduction pathways in smooth muscle cells. The latter focuses specifically on the role played by endothelin in mitogenesis. This is an important topic as endothelin is not just a vasoconstrictor, but has also been strongly implicated in disease-related remodelling of the vasculature and the airways.

In summary, this book provides an overview of endothelin research, and outlines evidence for its contribution to the pathology of a variety of cardiovascular diseases (congestive heart failure, atherosclerosis, myocardial ischaemia and infarction, stroke, pulmonary hypertension), some types of essential hypertension, and pre-eclampsia. Roles for the endothelins have also been suggested in asthma, acute and chronic renal failure, and prostatic disease. Currently, these are all areas for further investigation or clinical trials, the outcome of which will greatly influence our perception of the importance of endothelins in future years.

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