

Endothelial Vasoactive Substances and Cardiovascular Disease

Thomas F. Lüscher

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with a Foreword by Paul M. Vanhoutte

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Dedicated to my father

Dr. med. Emil Löscher

1904-1977

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Foreword

When Dr. Furchgott first reported that the presence of endothelium in isolated arteries profoundly modified their responsiveness to acetylcholine, few vascular pharmacologists and physiologists would have predicted how much this discovery eventually would effect their field of research. Indeed, in the last decade an ever increasing number of investigations have confirmed the original observation made in the rabbit aorta.

And we now realize that the principle of endothelium dependency of vascular responses is not only an ancestral characteristic of the vascular wall, but also an ubiquitous one, which expresses itself in many different ways. Indeed, where at first only endothelium-dependent relaxations were considered, it soon became apparent that endothelial cells also could generate vasoconstrictor signals. Both endothelium-dependent relaxations and contractions can be attributed to the secretion by the intimal cells of vasoactive substances, which have been called endothelium-dependent relaxing factor (EDRF) and endothelium-dependent contracting factor (EDCF), respectively. We now know that, in both cases, a single substance cannot explain all the phenomena of endothelium-dependent relaxation or contraction. It is very likely that the major EDRF is nothing else but nitric oxide and relaxes vascular smooth muscle as the nitrovasodilators by activation of the soluble guanylate cyclase. The exact nature of the other EDRF and EDCF(s) remains elusive. But, the possibility has begun to emerge that endothelial cells, by balancing the production of the EDRF(s) and EDCF(s), can exert a major role in the local control of vascular function. And this is obviously not only important under normal physiological conditions, but also in a variety of vascular diseases. Indeed, it now becomes apparent that in atherosclerosis, cerebral and coronary vasospasm and hypertension, endothelial cells lose their ability to generate EDRF(s) and/or is the EDRF that is no longer able to control vascular tone; in contrast, the ability to secrete EDCF appears unperturbed or even augmented. Hence, a switching from the predominance of endothelium-dependent dilatation to that of endothelium-dependent

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contraction may well be a major feature of vasospastic and hypertensive pathologies.

It should be emphasized that much of our understanding of the potential role of the unbalance between EDRF(s) and EDCF(s) as the mechanism underlying abnormal vascular responsiveness in hypertension has come from the work of Dr. Lüscher. Because he was one of the first to be confronted with the complexity generated by the simultaneous release of the two types of endothelial vasoactive substances, it is not surprising that he has a better grasp than most of the function of the endothelium as a controller of vascular tone. And, as always, what is well conceived is expressed clearly. This monograph represents a fine example of a very scholar by approach to a most difficult question. It contains a profusion of reference material for the curious minds who undoubtedly will be excited by this area of science and will want to know more about it. The illustrations, both data and schematics, are selected carefully to optimize the understanding of the reader. The text is clearly written and complete. The end product is a must for all interested in the vascular wall, whether they are cellular biologists, pharmacologists, physiologists or physicians treating patients with cardiovascular problems and hypertension.

I have had the rare privilege to be associated with Dr. Lüscher during several years. They were productive, as the author clearly is characterized by a total dedication to science and thoroughness. The association was not only scientifically most rewarding, but also personally most enjoyable. Hence, it is a rare pleasure to introduce this book to the readers. They will enjoy it!

Rochester, January 1988

Paul M. Vanhoutte, MD, PhD
Professor of Physiology and Pharmacology

Preface

Today numerous scientific publications appear every month and each week. Any author, therefore, faces the question whether his manuscript, review or book merits publication. Although only the future reader may judge, every author has to answer the question as well. Original research papers get their justification out of their originality and scientific quality. Unlike in the past, books are no longer reporting unpublished experiments or new observations; they rather review research in a given field or provide

physiological and pathophysiological concepts.

This monograph reviews the field of endothelium-derived vasoactive substances in physiology and their potential role in cardiovascular disease. This area of research has been dramatically stimulated by the remarkable observation of Furchgott and Zawadzki in 1980 demonstrating that the vascular endothelium may mediate relaxations of the underlying vascular smooth muscle cells by releasing endothelium-derived relaxing factor(s). Since then, endothelial research has expanded dramatically. Thus, it appears timely to review this new knowledge gained in the last decade. The present monograph tries to weight and position the data published so far, to set the knowledge of today in a common context for the use and stimulation of future research. Obviously, since this is a new area of cardiovascular research, a lot of questions remain unanswered; indeed, even the exact physiological role and importance of this remarkable cell has yet to be defined.

The first section of the monograph is devoted to the physiology of endothelium-derived vasoactive substances. Considerable species differences made it mandatory to devote a second section exclusively to endothelium-dependent responses in human blood vessels. Early on, the obvious potential of endothelium-mediated regulatory mechanisms in cardiovascular disease has prompted a large number of experimental studies. The potential impact of endothelium-mediated regulatory mechanisms in the pathophysiology of cardiovascular diseases, such as hypertension, atherosclerosis, coronary artery disease, cerebral vasospasm and

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diabetic vascular disease are described in a third section of the monograph. Hopefully, this review is able to convince the reader that endothelial cells may modulate vascular tone by releasing vasoactive substances in response to various stimuli and that these regulatory mechanisms may play a role in the pathophysiology of cardiovascular disease.

Basel, December 1987

Thomas F. Löscher

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