Volume 1

# The Physiology and Pharmacology of the Microcirculation

Edited by

NICHOLAS A. MORTILLARO

PHYSIOLOGIC AND PHARMACOLOGIC BASES OF DRUG THERAPY

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VOLUME 1

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1983

Academic Press

*A Subsidiary of Harcourt Brace Jovanovich, Publishers*
New York London
Paris San Diego San Francisco São Paulo Sydney Tokyo Toronto

ACADEMIC PRESS, INC.
111 Fifth Avenue, New York, New York 10003

*United Kingdom Edition published by*
ACADEMIC PRESS, INC. (LONDON) LTD.
24/28 Oval Road, London NW1 7DX

**Library of Congress Cataloging in Publication Data**

Main entry under title:

The Physiology and pharmacology of the microcirculation.

(Physiologic and pharmacologic bases of drug therapy)
Includes index.
1. Microcirculation. 2. Capillaries--Effect of drugs on. I. Mortillaro, Nicholas A. II. Series.
QP106.6.P48 1982 612'.135 82-20562
ISBN 0-12-508301-7 (v.1)

PRINTED IN THE UNITED STATES OF AMERICA

83 84 85 86 9 8 7 6 5 4 3 2 1

To my wife Mildred, daughter Susan, and son Philip

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# Foreword

Since the early 1960s, an enormous amount of information has been generated with regard to the physiopharmacology of the microcirculation. The present volumes are compilations of microcirculatory phenomena by renowned experts, who have integrated present knowledge into concise overviews concerning *(1)* how oxygen delivery is regulated by the tissues, *(2)* the biochemistry of smooth muscle and endothelial cells, and *(3)* the mechanisms associated with movement of fluid and molecules across capillary wall barriers.

The two volumes are organized such that the first five chapters of Volume 1 cover the biochemistry, metabolism, pharmacology, and physiology of the general microcirculation. Then, the microcirculation of 14 different organs is presented, with special emphasis on the metabolic needs of each organ as it carries out its functions. The action of different physiological hormones such as the prostaglandins on microcirculatory phenomena is integrated into the overall functional aspects of each organ's biochemistry, fluid balance, transcapillary solute exchange, blood flow, etc. Each contributor approaches the microcirculatory function of each organ using precise modeling ideas, and, although computer models are not included in these chapters, the reader can easily follow the developments along the lines of input–output functions, which have been analyzed away from a black-box approach, because each organ system is discussed relative to its biochemistry, special metabolic needs, functional requirements, and its role in the overall organism's scheme of energy–function balance.

Dr. Mortillaro is to be congratulated for developing such a cohesive and informative set of chapters. The information contained in these volumes promises to serve as factual material for many years to come, because the chapters

have sufficient depth to please the expert; they are also written in a style such that not only researchers but medical and graduate students will find the text most useful for learning the basic functional aspects of the microcirculation.

The *milieu internal* of Claude Bernard has not changed over the last century, yet our understanding of the regulatory phenomena associated with this milieu has expanded by orders of magnitude. A comparison of the effects of $PCO_2$ (or pH) on the cerebral circulation as compared to the peripheral vessels indicates how very differently organs can respond to the same stress, change of metabolic state, vascular pressure, etc. These volumes will give the reader a better appreciation and understanding of the complexities and interrelationships that exist within the body's vascular system as it works to provide nutrients to the many different types of functional cells. For the first time, the reader is treated to a physiological–pharmacological treatise on the microcirculation that focuses on the functional states and needs of each tissue as it relates to maintaining overall body hemostasis.

Aubrey E. Taylor

# Preface

This work, the first of two volumes on *The Physiology and Pharmacology of the Microcirculation,* brings together the expertise of many active and eminent investigators in the field. The approach taken in presenting the latest information in this vast field differs from that of other publications on the same subject, and in this respect it is unique. Whereas previous publications have dealt with microcirculation along functional lines, each chapter covering a specific function of many tissue beds and organs, the initial five chapters of the present volume present introductory, overall views of basic concepts regarding the microcirculation, with each of the remaining chapters covering a specific organ system. Hence, the reader whose knowledge of the microcirculation is limited may find it advantageous to concentrate first on the introductory chapters before moving on, whereas the experienced reader may wish to go directly to the chapter(s) dealing with a specific organ system(s).

Chapter 1 treats the biochemistry of isolated elements of the microvasculature, with special emphasis on the central nervous system. Chapter 2 brings into focus that microvascular element, the vascular smooth muscle, discussing not only ultrastructural characteristics, innervation, and contraction–relaxation, but also the effects of both endogenous and pharmacological vasoactive substances on vascular smooth muscle. Chapters 3 and 4 are concerned with the exchange mode of the microcirculation, the former concentrating on an overview of the mechanisms involved in the regulation of transcapillary fluid exchange, the latter focusing on the permeability of capillaries to small and large molecules in a variety of tissues. Chapter 5 concludes the introductory section with a consideration of the control mechanisms modulating microcirculatory dynamics.

Beginning with Chapter 6, the emphasis shifts to a consideration of the microcirculation in particular organs. Chapter 6 focuses on the cerebral circulation, considering not only the vascular anatomy, but also the regulation of cerebral blood flow in the adult, neonate, and fetus. In Chapter 7 the microcirculation of the eye is presented, with special emphasis on the part of its microcirculation responsible for providing the nutrition to the retina, that is, the retinal and choroidal circulation. Microcirculation of the heart is covered in Chapter 8, in which the functional anatomy, microcirculatory exchange, and the determinants of coronary blood flow are discussed. Finally, Chapter 9 concentrates on the microcirculation of the kidney, which is most directly related to the filtration of fluid into the tubular systems and the return of the tubular reabsorbate into the vascular system.

In Volume 2, the presentation of the microcirculation of particular organ continues with chapters on the lung, endocrine glands (with an emphasis on the salivary glands and exocrine pancreas), liver and spleen, stomach, small and large intestines, bone, skin, skeletal muscle, and the pathophysiology of the microcirculation.

I wish to thank the staff of Academic Press for their guidance and patience during the preparation of these volumes.

Nicholas A. Mortillaro

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*(in press)*

# Contents

# 1 Biochemical Mechanisms of the Microvasculature

Gene C. Palmer



## I. Introduction

Since the late 1970s techniques have been developed to isolate and culture capillaries from both central and peripheral tissues. With the advent of these methods a host of biochemical and pharmacogic investigations has



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ISBN 0-12-508301-7

helped to elucidate the physiologic and pathologic roles of the microcirculation. For various reasons the majority of the investigations have centered on the cerebral microvasculature, namely, capillaries, choroid plexus vessels, and pial vessels. The most obvious reason has been the enigma of the *blood–brain barrier*. Thus, capillaries have been considered to be the site of this perplexing structure. Capillaries in most regions of the brain have distinctive structural properties compared with capillaries in other organs. These special properties include overlapping endothelial cells jointed to one another by tight junctions, an absence of fenestrations in the endothelial cell wall, a paucity of pinocytotic vesicles, a high mitochondrial content, a lack of free permeability to water, a complete investiture of the capillary by astrocytic processes, the presence of monoamine nerve endings, a special complement of barrier enzymes, and carrier-mediated transport mechanisms. Regions of the brain not displaying evidence of a blood–brain barrier, that is, area postrema, pineal gland, and choroid plexus, contain capillaries that resemble those of peripheral organs. The choroid plexus, however, has tight junctions between the epithelial cells. In summation, the integrity of the capillary lining ensures that substances do not move in and out of the brain in an indiscriminate fashion but that, instead, their movement is a highly regulated process (see Raichle and Grubb, 1978; Hartman *et al.*, 1980; Cutler, 1980; Lindvall and Owman, 1980).

This chapter focuses principally on the biochemistry of isolated elements of the central microvasculature with reference made to isolated peripheral microvessels according to available data. These biochemical findings are correlated when possible to physiologic and/or pathologic conditions. The principal function of the capillary is to control the influx and efflux of substances into and out of the brain parenchyma. The choroid plexus is responsible for the formation and maintenance of the chemical composition of the cerebrospinal fluid. This structure also contains energy-dependent, saturable, and stereospecific processes to transport amino acids and metabolites. The pia-arachnoid likewise contains specialized mechanisms for transport but mainly removes substances from the brain by bulk flow mechanisms.

The movement of nonelectrolytes through cells of the blood–brain barrier and cerebrospinal fluid barriers may be regulated by passive diffusion, pinocytosis, or carrier transport. Passive diffusion occurs across a concentration gradient and depends on the lipid solubility and degree of ionization of the substance in question. Pinocytosis is not considered an important transport mechanism in cerebral capillaries; however, recent evidence indicates that neurohumoral transmission may control this system. The specialized carrier transport systems are the most important

function of the central capillaries in controlling the entrance and egress of materials into and from the brain. Facilitated transport systems exist for the influx and efflux of glucose. The system maintains a higher brain parenchymal level of glucose, probably as a safety factor. Small amino acids are removed from the brain by a sodium-dependent carrier, whereas the entrance of neutral and large amino acids is controlled by a unidirectional equilibrium system. Carrier systems are also present for ketones ($\beta$-hydroxybutyrate). This mechanism is inducible during starvation and serves also as a safety margin for energy during neonatal development. The influx of ketones is linked to another safety condition, the efflux of lactate and pyruvate, thereby controlling the brain pH environment under hypoxic situations. Special carrier-mediated systems are located in the choroid plexus for ascorbic acid and in the capillaries for tetrahydrofolic acid (for review see Cutler, 1980).

## II. Techniques for Isolation of Microvessels

Several methods have been developed to isolate relatively purified microvessels from a variety of tissues, especially from brain. When one is evaluating microvessels for biochemistry or pharmacology experiments, it is necessary to use preparations that are as pure as possible. For example, most capillary fractions contain red blood cells or mast cells, which possess unique metabolic characteristics. Preperfusion of the tissue with saline, balanced salt solutions, or appropriate buffers is one way of alleviating this problem. For brain tissues the pia must be removed, because it will isolate with the capillary fraction and in addition has different biochemical properties. Isolated cells should be monitored for purity by the use of phase-contrast microscopy and various enzyme markers; for example, alkaline phosphatase or $\gamma$-glutamyl transpeptidase can be determined either histochemically or biochemically. Some workers feel that isolation of cells with hyaluronidase, trypsin, or collagenase digestion adds further problems to biochemical analyses because of potential damage to the endothelium. The following discussion briefly outlines several popular methods, many of which are not difficult to perform.

### *A. Peripheral Endothelium*

Endothelium from a variety of tissues has been successfully isolated either by perfusing the tissue with digestive enzymes and centrifuging down the isolated endothelium or by mincing the tissue in a buffered