Textbook of Immunopharmacology

EDITED BY

M M DALE & J C FOREMAN

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EDITED BY

M. Maureen Dale
MB, BCh, PhD
Senior Lecturer in Pharmacology
University College, London

AND

John C. Foreman
PhD, MB, BS
Lecturer in Pharmacology
University College, London

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Dedication

This book is dedicated to Emeritus Professor Heinz O. Schild FRS, who introduced us to immunopharmacology, and also to our students whose critical and stimulating participation in the course over the years has encouraged us to produce this book.

List of Contributors

G. L. ASHERSON MA, DM, FRCP, FRC Path, BCh, Division of Immunological Medicine, Clinical Research Centre, (Medical Research Council), Harrow, Middx HA1 3UJ, UK

E. S. K. ASSEM MB, BCh, PhD, MRCP, Department of Pharmacology, University College London, Gower Street, London WC1E 6BT, UK

M. K. BACH PhD, Department of Hypersensitivity Diseases Research, The Upjohn Company, Kalamazoo, MI 49001, USA

R. BOMFORD BA, PhD, Department of Experimental Immunobiology, Wellcome Research Laboratories, Langley Court, Beckenham, Kent BR3 3BS, UK

J. R. BOOT PhD, Lilly Research Centre, Erl Wood Manor, Windlesham, Surrey, UK

J. F. BOREL PhD, Preclinical Research, SANDOZ Ltd., CH 4002 Basle, Switzerland

C. G. COCHRANE MD Department of Immunology, Scripps Clinic and Research Foundation, 10666 North Torrey Pines Road, La Jolla, CA 92037, USA

M. M. DALE MB, BCh, PhD, Department of Pharmacology, University College London, Gower Street, London WC1E 6BT, UK

P. DAVIES PhD, Department of Immunology and Inflammation, Merck Institute for Therapeutic Research, Rahway, N.J. 07065, USA

W. DAWSON PhD, Lilly Research Centre, Erl Wood Manor, Windlesham, Surrey, UK

R. J. FLOWER PhD, Department of Prostaglandin Research, Wellcome Research Laboratories, Langley Court, Beckenham, Kent BR3 3BS, UK

J. C. FOREMAN PhD, MB, BS, Department of Pharmacology, University College London, Gower Street, London WC1E 6 BT, UK

L. G. GARLAND PhD, Department of Pharmacology, Wellcome Research Laboratories, Langley Court, Beckenham, Kent BR3 3BS, UK

J. M. HANSON PhD, Department of Clinical Pharmacology, Cardiothoracic Institute, (University of London), Fulham Road, London SW3 6HP, UK

P. M. HENSON PhD, Department of Paediatrics, National Jewish Hospital and Research Centre, & Department of Pathology and Medicine, University of Colorado Health Sciences Centre, Denver, CO, USA

G. A. HIGGS PhD, Department of Prostaglandin Research, Wellcome Research Laboratories, Langley Court, Beckenham, Kent BR3 3BS, UK

H. F. HODSON PhD, Department of Chemistry, Wellcome Research Laboratories, Langley Court, Beckenham, Kent BR3 3BS, UK

A.B. KAY MB, BCh, PhD, DSc, MRCP, MRC Path, Department of Clinical Immunology, Cardiothoracic Institute, (University of London), Fulham Road, London SW3 6HP, UK

C. J. MEADE PhD, Lilly Research Centre, Erl Wood Manor, Windlesham, Surrey, UK

J. L. MONGAR PhD, Department of Pharmacology, University College London, Gower Street, London WC1E 6BT, UK

M. MOORE PhD, MRC Path, Department of Immunology, Paterson Laboratories, Christie Hospital and Holt Radium Institute, Manchester M20 9BX, UK

J. MORLEY PhD, MRC Path, Department of Clinical Pharmacology, Cardiothoracic Institute, (University of London), Fulham Road, London SW3 6HP, UK

M. PLAUT MD, Department of Medicine, Johns Hopkins University School of Medicine, 5601 Loch Raven Boulevard, Baltimore, MD 21239, USA

V. M. RUMJANEK PhD, Department of Clinical Pharmacology, Cardiothoracic Institute, (University of London), Fulham Road, London SW3 6HP, UK

R. J. SMITH PhD, Department of Hypersensitivity Diseases Research, The Upjohn Company, Kalamazoo, MI 49001, USA

D. R. STANWORTH PhD, DSc, FRC Path, Department of Immunology, University of Birmingham, Birmingham B15 2TJ, UK

J. R. WALKER PhD, DSc, Lilly Research Centre, Erl Wood Manor, Windlesham, Surrey, UK

M. A. WASSERMAN PhD, Department of Hypersensitivity Diseases Research, The Upjohn Company, Kalamazoo, MI 49001, USA

R. C. WIGGINS MRCP, Department of Medicine, University of Michigan Medical School, Ann Arbor, MI 48109, USA

P. C. WILKINSON MD, Department of Bacteriology and Immunology, University of Glasgow, Glasgow G11 6NT, UK

T. J. WILLIAMS PhD, Department of Pharmacology, Institute of Basic Medical Sciences, (University of London), Royal College of Surgeons of England, Lincoln's Inn Fields, London WC2A 3PN, UK

L. J. F. YOULTEN MD, BS, PhD, Department of Medicine, Guy's Hospital Medical School, London SE1, UK

Preface

This book is based on the immunopharmacology course for third year BSc students in the pharmacology department of University College London. In giving the course we have felt handicapped by the fact that there was no simple text to form a basis for the seminars and discussions and from which the students could start their forays into the literature. It is primarily to fill this gap that this book has been written, but we are aware that there is a growing interest in immunopharmacology and we feel that an introductory text will be of value to biologists from other disciplines coming new to this field. Chemists, and medicinal chemists with a limited background in biology should also find this a useful introduction.

For those who have little or no knowledge of immunology, pathology or histology we have written an introductory chapter which gives an outline of the pharmacological approach to the interaction between mammalian host and pathogen or noxious agent—the inflammatory response. This first chapter sets the scene for the main body of the book, which, in four sections, deals with the cells, the mediators, the main local and systemic phenomena of inflammation, and the drugs which influence it.

M. M. Dale
J. C. Foreman

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Chapter I

Introduction to the immunology and pathology of host defence mechanisms

M. M. DALE & J. C. FOREMAN

Immunopharmacology is that area of biology where immunology, pathology and pharmacology overlap. It concerns the pharmacological approach to the interaction of mammalian host with noxious agent or invading pathogen.

A mammalian organism faced with the threat of invasion by a pathogen (disease causing organism) can call on an extensive repertoire of defensive responses. When these are effectively deployed the result is either a rapidly resolving lesion (e.g. a boil which heals) or no lesion at all (e.g. smallpox infection in a vaccinated host). When they are excessively or perhaps inappropriately deployed the responses may cause damage to the host and may themselves constitute part of the disease process (e.g. in lobar pneumonia or rheumatoid arthritis). An impressive variety of chemical mediators produced by the host controls or modulates the responses in the repertoire and this is one of the main aspects of the host/pathogen interaction which is of interest to the pharmacologist.

In essence, the approach is that which has proved of value in the investigation of chemical transmitters of the nerve impulse in the autonomic and peripheral nervous system. Here the use of drugs (e.g. eserine, atropine, tubocurarine) was necessary for the investigation of the possible role of a chemical transmitter (acetylcholine). Information so gained made possible the development of further drugs (e.g. hexamethonium, succinylcholine), which, used not only therapeutically but also as tools, facilitated further understanding of nervous transmission and the subsequent development of further drugs; and the process continues.

In the area of interaction of mammalian host and pathogen, the problem is vastly more complex because of the multiplicity of mediators, but the contribution of the pharmacological approach can nevertheless be of considerable value. Indeed it has already proved so; the investigation of the mode of action of aspirin, a drug which had been introduced empirically, has led to the elucidation of the possible role of arachidonate metabolites as mediators in inflammation and this may give rise to valuable new drugs.

In this first chapter we outline in very simple terms the series of events

which may take place locally when a microorganism gains access to the tissues of a mammalian host, and we explain the plan of the rest of the book. We will be describing a hypothetical situation, but a rough approximation would be a staphylococcal infection causing an acute inflammatory response (e.g. a boil). We describe first the reactions which do not involve any immunological mechanisms and then consider how these reactions could be sharpened and made more selective by the specific immunological response. However it must be borne in mind that our main concern is about those situations in which the reactions to be described are either excessively or inappropriately deployed in response not only to microorganisms, but to substances from within or from outside the body which are in reality innocuous, but which are treated as noxious agents.

The inflammatory response

In essence, the changes can be divided into vascular events and cellular events.

Vascular events

These may start immediately and develop during the first few hours. They comprise dilatation of the blood vessels with increased blood flow, followed by slowing of the blood, increased vascular permeability and exudation of plasma. The plasma contains numerous substances which can act as mediators of the reaction against the 'invader'. Among these substances are the components for three enzyme cascades: the coagulation system, the complement system and the kinin system. The activation of all these systems involves limited proteolysis.

The fluid exudate is absorbed into the lymphatics and, carrying with it the invading microorganism or its products, passes to the local lymph glands or lymphoid tissue where an immune reaction may be initiated (see below).

The coagulation system consists of several proteins, most of which are pre-enzymes, forming a 'cascade' in which activation of small amounts of the first pre-enzyme ('Hageman' factor or factor XII) triggers larger amounts of the second in the sequence, which in turn activates even more of the next one, and so on. The response can thus be quickly amplified and result in the rapid formation of effective concentrations of *thrombin*, the main enzyme. Trombin acts on the fibrinogen in solution in plasma to produce insoluble strands of fibrin which form a meshwork. When this process occurs in whole blood the meshwork is the basis of the blood clot which consists of

the cells of the blood, especially red cells, trapped in the mesh. In a host/pathogen interaction in the tissues such as we are considering, there may be few red cells and the fibrin is laid down on its own and may serve to limit spread of the infection.

Activated Hageman factor, in addition to starting off the blood clotting cascade, also triggers the fibrinolytic system, which is another related cascade. It does this by activating the enzyme plasminogen activator, which generates plasmin, another enzyme, and a destroyer of fibrin. In breaking down fibrin, plasmin releases peptides which are chemotactic for white cells (i.e. attracts them). Hageman factor also activates the kinin system (see below). Plasmin can act on activated Hageman factor to make it more effective in triggering the kinin system and less effective in the clotting cascade.

The complement system is also an enzyme cascade. Its activation produces several factors which can be shown, *in vitro*, to have powerful effects on blood vessels, leucocytes, other tissue cells and microorganisms. The cascade consists of 9 major components, designated C1 to C9. The important event is the activation of C3, which is present in the plasma in relatively high concentration (more than 1 mg/ml). It may be activated in two main ways: (a) the classical pathway—through binding of antibody to C1 and (b) the alternative pathway—through numerous non-antibody-mediated stimuli such as substances derived from microorganisms (e.g. yeast cell wall polysaccharides, endotoxins, etc.) which activate the alternative pathway of complement generation. The products of C3 activation have a variety of actions. They stimulate mast cells to secrete mediators, have chemotactic activityfor white blood cells, attach to the surface of microorganisms and facilitate their ingestion by white blood cells. They can also stimulate macrophages to secrete lysosomal enzymes, and mobilize white blood cells from the bone marrow.

C3 activation is followed by the activation of C5, which releases another produce, C5a. C5a in addition to causing histamine release is powerfully chemotactic for white blood cells and activates and causes release of lysosomal enzymes from some of them.

Assembly of the later complement components C5 to C9 on the bacterial wall or cell membrane leads to lysis of the bacterium or cell. Thus complement mediates killing of invading bacteria or damage to multicellullar organisms and sometimes to the host's own cells.

The central event in the complement cascade—activation of C3—can also be brought about by the main enzymes of the coagulation and fibrinolytic cascades, thrombin and plasmin.

There will be further discussion of the biological activities of the complement system in Chapter 11.

The kinin system is another enzyme cascade. A pre-enzyme present in blood can be activated by Hageman factor, plasmin, neutrophil and macrophage lysosomal proteases or by dilution, to give kallikrein, a proteolytic enzyme. Kallikrein splits off a pharmacologically active polypeptide, a kinin, from α-globulins in the plasma. The kinins are powerful vasodilators and also increase vascular permeability. In addition they cause pain. Kinins can also be shown to stimulate prostaglandin production (see below) and kallikrein itself is chemotactic for neutrophils *in vitro*.

The kinin system and its interaction with Hageman factor will be dealt with in Chapter 12. Other powerful mediator systems come not from the blood but from cells and will be discussed below.

Cellular events

Some of the cells involved are already present in the tissues—the mast cells and tissue mononuclear phagocytes—while others enter the area from the blood. These latter, the leucocytes or white cells of the blood, are actively motile cells and are of two types:

1. The polymorphonuclear cells (cells with many lobed nuclei) which are subdivided into neutrophils, eosinophils and basophils on the basis of the staining properties of the granules in their cytoplasm. These cells are sometimes referred to as granulocytes.
2. The mononuclear cells (or cells with single, non-lobed nuclei) which are subdivided into monocytes and lymphocytes.

MAST CELLS

These cells are uniquely placed at the sites of possible entry into the tissues of pathogen or noxious agent: near skin surfaces, close to the mucous membranes lining body cavities and around blood vessels. They are capable of secreting or generating an array of mediators which have the capacity to modify vascular and cellular reactions as well as to affect some of the plasma factors. Mast cells have receptors for antibody and for complement components as constituents of the cell membrane. They may be activated to secrete mediators not only through these receptors, but also by factors produced by neutrophils. They may also release mediators after direct physical damage.

The main substance released by the mast cells is histamine, which, through receptors which are termed H1 receptors, can dilate blood vessels, increase vascular permeability and contract smooth muscles such as that in the bronchioles and the gut. Histamine may in addition modulate the responses of other cells, possibly through other histamine receptors. The

mast cells also release other mediators, including a complex sulphated mucopolysaccharide (heparan or heparin) which may inhibit blood clotting and can also neutralize some of the pharmacologically active cationic proteins that are released from neutrophils and other cells. The mast cell is described in Chapter 2 and histamine in Chapter 8.

THE POLYMORPHONUCLEAR LEUCOCYTES (POLYMORPHS)

These cells are the first of the leucocytes on the scene of the inflammatory reaction. In man they make up about 60% of the white cells of the blood. They are end cells with no ability to multiply, little capacity for protein synthesis, and a short life span. They adhere to the sides of the blood vessels in the area, then actively migrate through the wall of the vessel to the site of the invading pathogen. Neutrophils, in particular, are capable of engulfing, killing and digesting microorganisms. They, and the eosinophils have receptors on their surfaces for one of the products of complement activation which adheres to the surface of bacteria or multicellular parasites. This product, C3b, forms a link between polymorph and invading organism. (A further link may be made by antibody; see below.) Neutrophils contain within their granules an array of digestive enzymes which can deal with virtually all the structural components of most microorganisms. These enzymes work best at the low pH found in lysosomes. Neutrophils may in some circumstances actively secrete the constitutents of their granules, among which are enzymes which work best at the neutral pH of body fluids and which can cleave complement components and start the kinin cascade. Thus the participation of the neutrophils provides another method for activating these powerful systems of mediator production. When the secretory process is inappropriately triggered, these and other active agents of the granules may cause unwanted damage to the host's own tissues.

Eosinophils are apparently more important in the defence against helminths than microorganisms.

The neutrophil is dealt with in Chapter 3, the eosinophil is in Chapter 5 and the basophil is considered along with the mast cell in Chapter 2. Some aspects of the general leucocyte response to infection will be dealt with in Chapters 17 and 19.

THE MONOCYTES

These appear on the scene at a later stage of the reaction, many hours after the polymorphs. In the tissues they transform into macrophages (literally 'big eaters', as compared to the polymorphs which were originally called 'microphages' or 'little eaters'). Other similar types of cell, all belonging to

the category or 'mononuclear phagocytes' are present in various tissues, probably derived originally from blood-borne monocytes. They engulf not only microorganisms but tissue debris and dead polymorphs. They have a role in presenting antigenic material to lymphocytes in the initiation of an immune response. They can secrete not only lysosomal enzymes, but complement components, prostaglandins, a tissue factor which can start the coagulation cascade, interferon, a fibroblast-stimulating factor, pyrogen and factors which modify the activities of lymphocytes. They are important in repair processes and when stimulated by glucocorticoids they secrete macrocortin, a polypeptide which inhibits the inflammatory response. Mononuclear phagocytes are dealt with in Chapter 6, and aspects of their actions are also covered in Chapters 7 and 13.

Mediators derived from cells

ARACHIDONATE METABOLITES

When the cells described above are stimulated or damaged, another major mediator system is generated, by phospholipase A_2, from arachidonic acid present in the phospholipids in the cell membranes. Arachidonic acid is metabolized by several pathways, the amount dealt with via each pathway depending mainly on the cell type. One pathway gives rise to thromboxane (which has vasoconstrictor and platelet aggregating actions), prostacyclin (which has vasodilator and platelet disaggregating action) and various prostaglandins (PGs). Some prostaglandins of the E series, have vasodilator actions and also potentiate the actions of agents which cause increased vascular permeability and pain. In addition they inhibit the activity of some inflammatory cells. Other prostaglandins may cause spasm of bronchial smooth muscle. The pathway which gives rise to these PGs starts with the action of a cyclo-oxygenase enzyme, and is a major route of arachidonate metabolism in macrophages.

Another pathway starts with the action of a lipoxygenase and gives rise first to hydroperoxyeicasotetraenoic acids (HPETEs) and then either to hydroxyeicasotetraenoic acids (HETEs) or to leukotrienes. One of these, leukotriene B_4 (LTB_4) is a very potent chemotactic agent for neutrophils, eosinophils and macrophages and also stimulates neutrophils to secrete. Others, LTC_4 and LTD_4, have powerful bronchoconstrictor actions and very probably together constitute the substance previously known as 'slow reacting substance of anaphylaxis'. Polymorphs metabolize arachidonate mainly to HETEs and LTB_4, while phagocytosing macrophages and possibly mast cells produce LTC_4 and LTD_4, as well as PGs. Arachidonate metabolites are dealt with in Chapter 9.