

THE PHARMACOTHERAPY OF INFLAMMATION

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Summary

Throughout the world, inflammatory disorders are a major cause of morbidity and mortality, and consequently many pharmacological approaches have been developed to treat them. This chapter will describe the basic features of inflammatory disease, deal with the pharmacology of the drugs used in inflammatory conditions and then discuss specific uses of anti-inflammatory agents in individual conditions. An emphasis will be placed on approaches at the different hierarchical levels of the inflammatory response and the use of combined therapies, depending upon disease severity and persistence.

1. Introduction

Inflammation is a broad descriptor that has different meanings in different contexts. Whilst this chapter deals with anti-inflammatory drugs, it is important to remember that the inflammatory process is a key innate protective mechanism that serves to reduce the likelihood and/or severity of infection and promote tissue repair. Anti-inflammatory drugs are commonly used when inflammation is triggered inappropriately, is poorly resolved becoming chronic in nature, or reaches a severity that is debilitating.

Let's first discuss the features of inflammation at the level of tissues. The process of inflammation is initiated upon tissue damage. This damage may result from mechanical trauma, exposure to harmful chemicals or toxins, local infection with a pathogen that triggers an innate or adaptive immune response, or an autoimmune response. Initial aspects of inflammation are dominated by a vascular component.

These features can be most easily visualized in the skin, although essentially identical processes take place in the less superficial tissues. The regional dilatation of blood vessels results in an increase in blood flow that will manifest as reddening. The blood vessels also become leaky under the influence of many of the same mediators that cause vasodilatation. The leakiness involves the formation of inter-endothelial gaps through which plasma can flow according to the hydrostatic pressure gradient.

This is to be distinguished from true increases in vessel permeability, whereby there is an increase in solute and solvent transfer across the intact endothelium by diffusional mechanisms. There are both mechanical and biochemical consequences of this increase in plasma flow into the tissue. When the accumulation of leaked plasma exceeds the capacity of the lymphatic drainage, the build-up of fluid increases the pressure inside the tissue and causes swelling. This swelling may restrict function, in a joint for instance, or can lead to pain via activation of stretch receptors on sensory nerves.

The biochemical consequences include the delivery into the tissue of precursors to powerful inflammatory mediators including thrombin, bradykinin and activated complement. The formation of these inflammatory products requires the activation of proteolytic cascades that are also triggered and fuelled by plasma exudation and exposure to non-vascular tissue components.

The actions of inflammatory mediators released early in the response also serve as a stimulus for the triggering of a strong immune cell inflammatory component. Thus, leukocytes are recruited selectively to the area of tissue damage, are activated and migrate from the blood into the tissue. Infiltration of these cells into the tissues is assisted by the vascular changes described above.

Once activated, these cells are a major source of inflammatory mediators, which include numerous cytokines with potent and broad-ranging activities. This cellular immune response instigates immediate protection from pathogens through innate responses, whilst priming adaptive immunity for longer term, more specific protection, should that be necessary. It should also be remembered that activated vascular endothelial cells and other non-immune cells around the area of tissue damage are also capable of secreting mediators with inflammatory capabilities. Figure 1 outlines the vascular and cellular features of the inflammatory response.

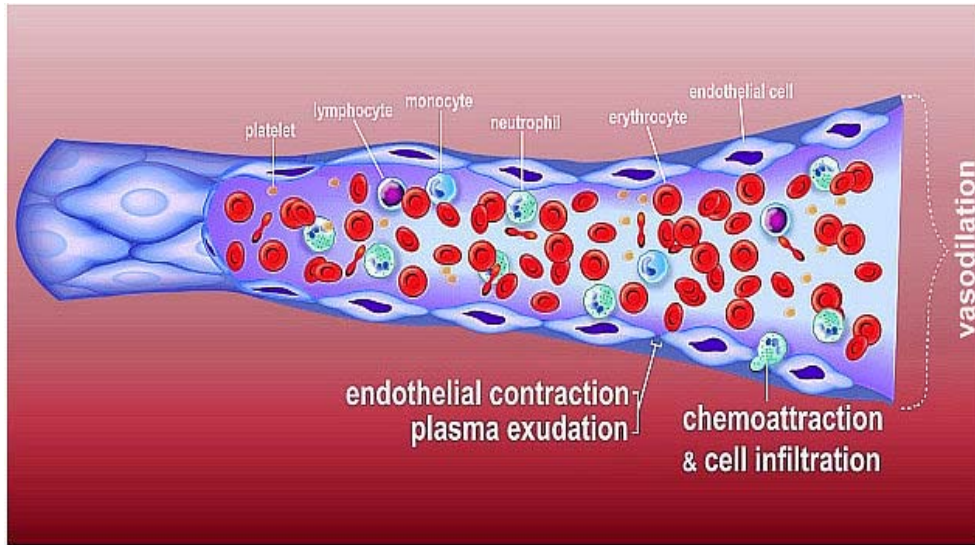


Figure 1. Vascular changes occurring during inflammation. Upon tissue injury, inflammatory mediators trigger vasodilation and enhanced vascular leak resulting in the characteristic inflammatory features of reddening and edema. Many inflammatory mediators also enhance adhesion molecule expression on endothelial cells and moreover serve as chemotactic factors for leukocytes such as neutrophils. Under normal circumstances, leukocyte recruitment reduces the likelihood of infection, leads to removal of cell debris and facilitates tissue repair.

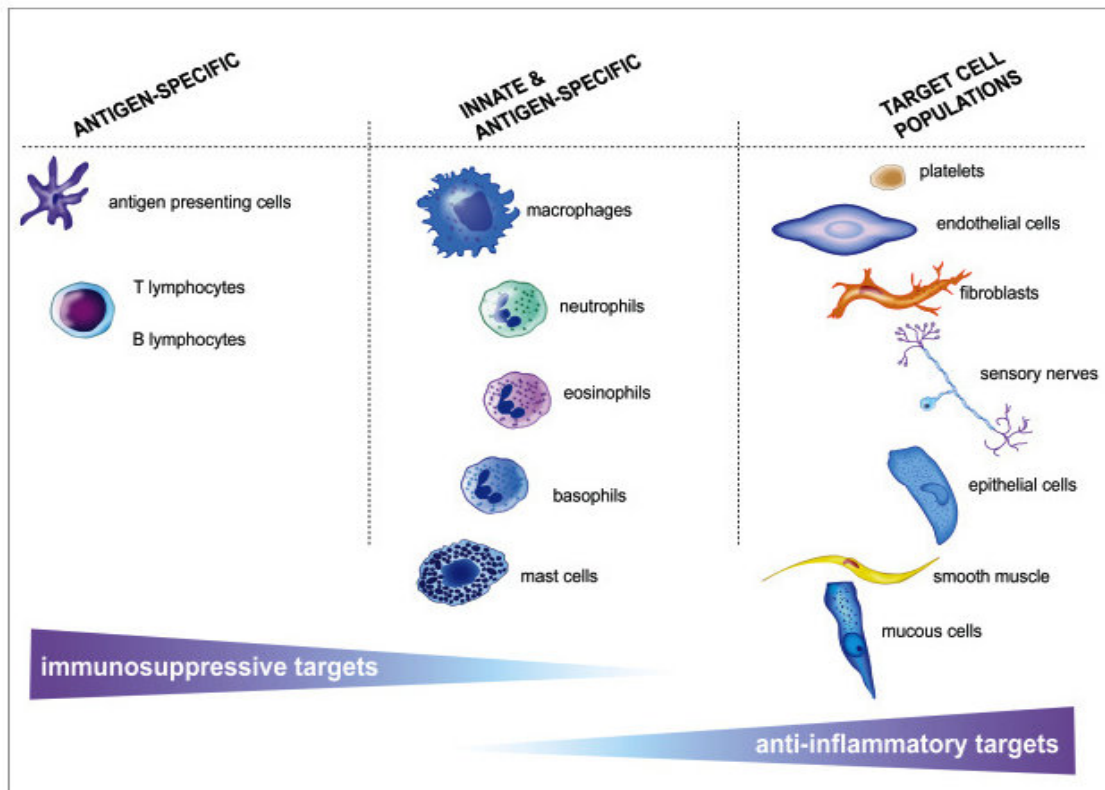


Figure 2. Drugs used to treat inflammation target different hierarchical levels of the immune system. Depending on disease severity and chronicity, a variety of agents can

be used to dampen inflammation. Clearly the hierarchical level of the target will determine the downstream consequences of its modulation. Drugs that prevent the actions of inflammatory mediators on target cell populations (e.g. anti-histamines) are effective in relatively mild and acute indications. Drugs that target key antigen-driven processes, such as the activation of lymphocytes (e.g. cyclosporine), have profound immunosuppressant actions and are thus used in the chronic inflammatory disease setting. Whilst these latter agents have potent anti-inflammatory activity, they also usually possess more troublesome unwanted effects.

Dampening the actions of inflammatory mediators is the goal of the various clinically utilized anti-inflammatory drugs. Anti-inflammatory activity can be achieved at numerous hierarchical levels of the inflammatory response. Thus, drug targets range from blocking the actions of specific mediators with receptor antagonists or inhibiting enzymes involved in mediator synthesis, to broad inhibition of immune responses with immunosuppressant drugs. The use and effectiveness of any particular drug is determined by numerous factors that include the cause and severity of the disease, the tissue sites affected, functional 'redundancy' and 'synergy' amongst inflammatory mediators (discussed later), and the unwanted effects of the drugs chosen. Figure 2 illustrates a "hierarchical" viewpoint of the cells and processes involved in an inflammatory response. This provides a framework for the sites of action of the anti-inflammatory drugs discussed later.

The next section will describe the major mediators involved in the inflammatory response and their origins, cellular or otherwise. We will also give a brief mention to endogenous inhibitors of inflammation. Although these negative regulators are in most instances considerably less well understood than their pro-inflammatory counterparts, their dysfunction might also underlie inflammatory disorders. A clearer understanding of their roles may provide new avenues for future drug design and development.

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Biographical Sketches

Alastair Stewart was awarded BScHons and PhD degrees from the University of Melbourne, Australia. He carried out a postdoctoral period in Prof Priscilla Piper's laboratory at the Royal College of Surgeons, in London, returning to Melbourne in 1986. He has held appointments in the Department of Physiology and at the Bernard O'Brien Institute of Microsurgery before returning to the Department of Pharmacology in 1998, where he is currently appointed Professor. His research interests are varied, but have been directed towards understanding the role of inflammatory mediators in complex, chronic tissue remodeling, such as occur in asthma, pulmonary fibrosis and solid tumors.

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He has worked as a research fellow at The Randall Institute, Kings College London, UK and in The Department of Pathology, University of New Mexico, USA. He relocated to Australia first as a Lecturer in Pharmacology at the University of the Sunshine Coast, Queensland before moving to his present position at the University of Melbourne, Australia. His main areas or research interest are allergic inflammatory disease and mast cell biology with a focus on cellular signal transduction. He teaches broadly in the discipline of Pharmacology to both undergraduate and postgraduate students.

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