ANTIFIBRINOLYTIC DRUGS

Chemistry, Pharmacology and Clinical Usage

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Preface

Drugs which inhibit the action of the fibrinolytic system have been available for around twenty-five years. Initial enthusiasm for their use in the management of bleeding, both generalized and local, and a wide variety of other conditions has been replaced by a more critical assessment of their therapeutic indications. This volume reviews the accumulated knowledge of the chemistry and pharmacology of the antifibrinolytic drugs and describes their past and present clinical usage with particular reference to the information gained from controlled clinical trials. The current state of knowledge of the fibrinolytic system is detailed as a background for an understanding of the mechanism of the action of the drugs, the rationale for their use and the possible effects of reduced production of the fibrinolytic enzyme plasmin.

It is hoped that this book will be of interest and benefit to pharmacologists and clinicians considering the use of antifibrinolytic drugs in the management of bleeding and other disorders.

Contents

CHAPTER ONE

Introduction

OUTLINE OF HAEMOSTATIC MECHANISM

Haemostasis is achieved normally through the co-operative interactions between the wall of the damaged blood vessel, platelets and the coagulation system. Injured vessels constrict, reducing blood flow to the site of the bleeding, while platelets adhere to the subendothelial structures exposed in the wall of the damaged artery or vein, in particular, collagen. Adhesion is accompanied by activation of the platelets, resulting in a series of intraplatelet reactions that lead to the secretion of adenosine diphosphate and other materials from the platelet granules and to the formation of thromboxane A_2 from the arachidonic acid derived from the platelet membrane phospholipid. Both adenosine diphosphate and thromboxane A_2 are potent inducers of platelet aggregation, the term applied to the cohesion of platelets to each other. Through this sequence a plug of platelets is formed, normally capable of sealing the breach in the wall of the injured vessel. This platelet plug, however, is unstable and liable to be dislodged by the flowing blood resulting in further bleeding unless stabilized by the formation of a supportive network of fibrin through the action of the coagulation mechanism.

The formation of insoluble threads of fibrin from the circulating soluble fibrinogen is the result of a complex sequence of reactions culminating in the explosive production of thrombin at the required site. There are two pathways leading to the formation of thrombin, known as the intrinsic and extrinsic coagulation pathways. Although these pathways are separate, there are a number of interconnections between them. The intrinsic pathway is initiated by the interaction of factor XII (Hageman factor) with a negatively charged surface such as collagen and involves the participation of prekallikrein and high molecular weight kininogen. In this reaction the inactive precursor form of factor XII is converted to its enzymatic form (factor XIIa) which is capable of activating factor XI, present both in plasma and adsorbed on the

surface of platelets. The activated factor XI proceeds to activate factor IX which is bound to the negatively charged phospholipid surface of the platelet through calcium bridges. On this surface the molecules are aligned through factor VIII (antihaemophilic globulin) with those of factor X, also attached to the platelet surface via calcium bridges, to bring about the activation of the factor X. Prothrombin, in turn aligned in optimum position with the activated factor X through factor V, is activated to thrombin. Factor V is present in the platelet granules and can be secreted from them. Both factor VIII and factor V are converted to a functionally active form by thrombin, acting in a positive feedback manner. The extrinsic pathway is initiated by the liberation of tissue factor, present in most tissues, on injury. The interaction of factor VII with tissue factor results in a form of factor VII which can activate factor X, allowing the formation of thrombin through the common pathway involving factor V and prothrombin. Thrombin is capable of cleaving two specific fibrinopeptides from the fibrinogen molecule to form fibrin monomers which undergo polymerization with the production of an insoluble fibrin network. In the final stage of the coagulation mechanism the fibrin polymers are stabilized by the formation of covalent bonds through the action of factor XIII (fibrin-stabilizing factor). The contribution of the platelet surface phospholipid, the association of clotting factors with platelets, and the activating effect of damaged tissues all lead to localization of the coagulation process to the site of injury and the platelet plug. The fibrin formed serves to stabilize the platelet mass and achieve permanent haemostasis. The reactions of the coagulation mechanism are summarized in diagrammatic form in Figure 1.

A number of plasma proteins with an inhibitory action on one or more of the activated clotting factors contribute to the control of the coagulation mechanism. The major inhibitors are probably antithrombin III and $C\bar{1}$ inactivator. Antithrombin III is capable of neutralizing a number of activated clotting factors, particularly after its reaction with heparin. C1 inactivator has the ability to inhibit the activated forms of the factors participating in the early phases of the intrinsic pathway. The recently identified protein C can inactivate the proteolytically altered forms of factors V and VIII.

A more extensive coverage of the components of the physiological haemostatic mechanism and their interactions may be found elsewhere (for example, Ogston, 1983).

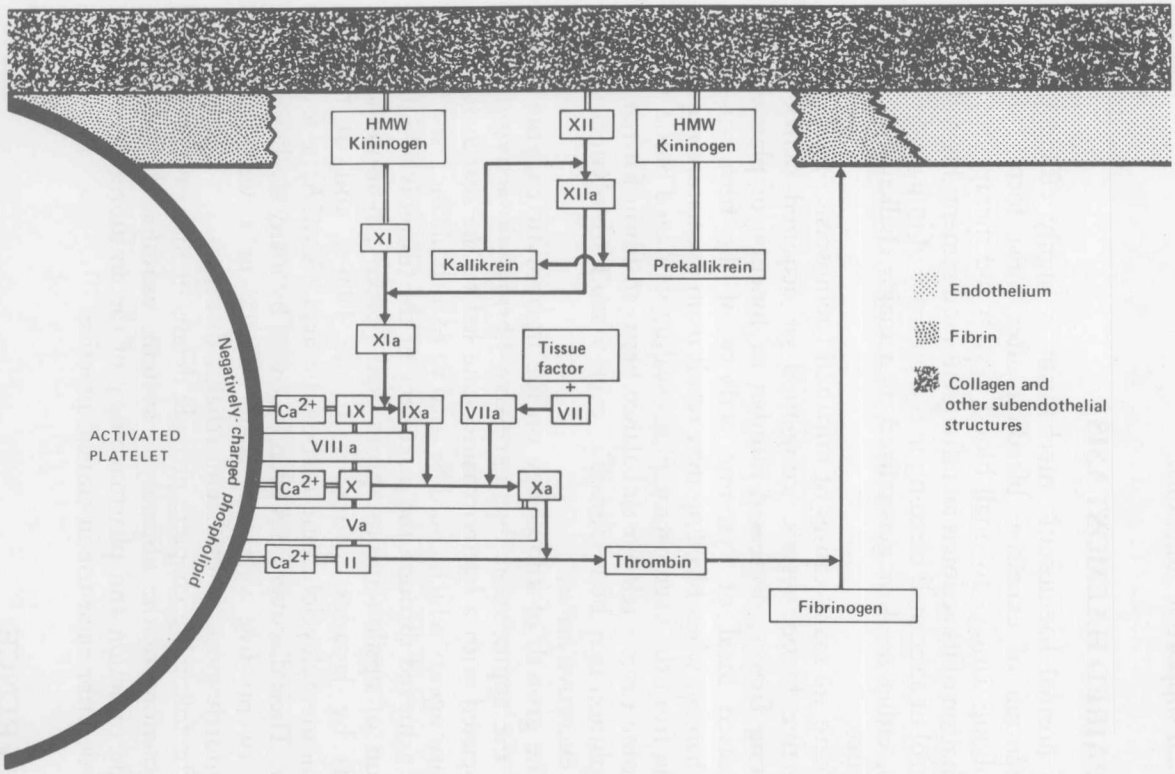

Figure 1. Schematic representation of the coagulation mechanism

The fibrinolytic system, considered in detail in Chapter 2, is concerned with the removal of fibrin after it has completed its normal supportive functions.

IMPAIRED HAEMOSTASIS

The normal haemostatic mechanism is highly efficient in the prevention of excessive bleeding after most forms of injury involving damage to small blood vessels and therapeutic supplementation of its action is an infrequent requirement. However, the control of abnormal bleeding in the presence of impaired haemostasis, either local or generalized, is a major challenge in clinical practice.

There are many causes of impaired haemostasis. These include defective blood vessels, congenital or acquired deficiency of clotting factors, decreased number or function of platelets, and increased local or systemic activity of the fibrin-dissolving mechanism when bleeding may result from premature removal of fibrin from the haemostatic plugs sealing damaged blood vessels. In some cases a relative imbalance between fibrin formation and dissolution may be responsible, even when fibrinolytic activity is not excessive *per se*.

The growth of knowledge on the fibrinolytic enzyme system and the appreciation that excessive fibrinolytic activity can be associated with a haemorrhagic state led to the search for therapeutic agents which could be used to reduce fibrinolysis. Success was achieved through the discovery of the fibrinolysis-inhibiting action of epsilon-aminocaproic acid (EACA; 6-aminohexanoic acid) by Japanese workers in the 1950s, and of *trans-p*-aminomethylcyclohexane carboxylic acid (AMCA) a few years later. Their discovery has been followed by many studies over the last twenty-five years on their efficacy in a wide range of haemorrhagic and non-haemorrhagic disorders.

The following chapters provide details of the components and interactions of the fibrinolytic system, examine the chemistry, mode of action and pharmacology of the antifibrinolytic drugs, and describe their use in clinical practice.

REFERENCE

Ogston, D. (1983) *The Physiology of Hemostasis*, Croom Helm, London.