HOMEOSTATIC CONTROL OF BLOOD COAGULATION

Essay

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by

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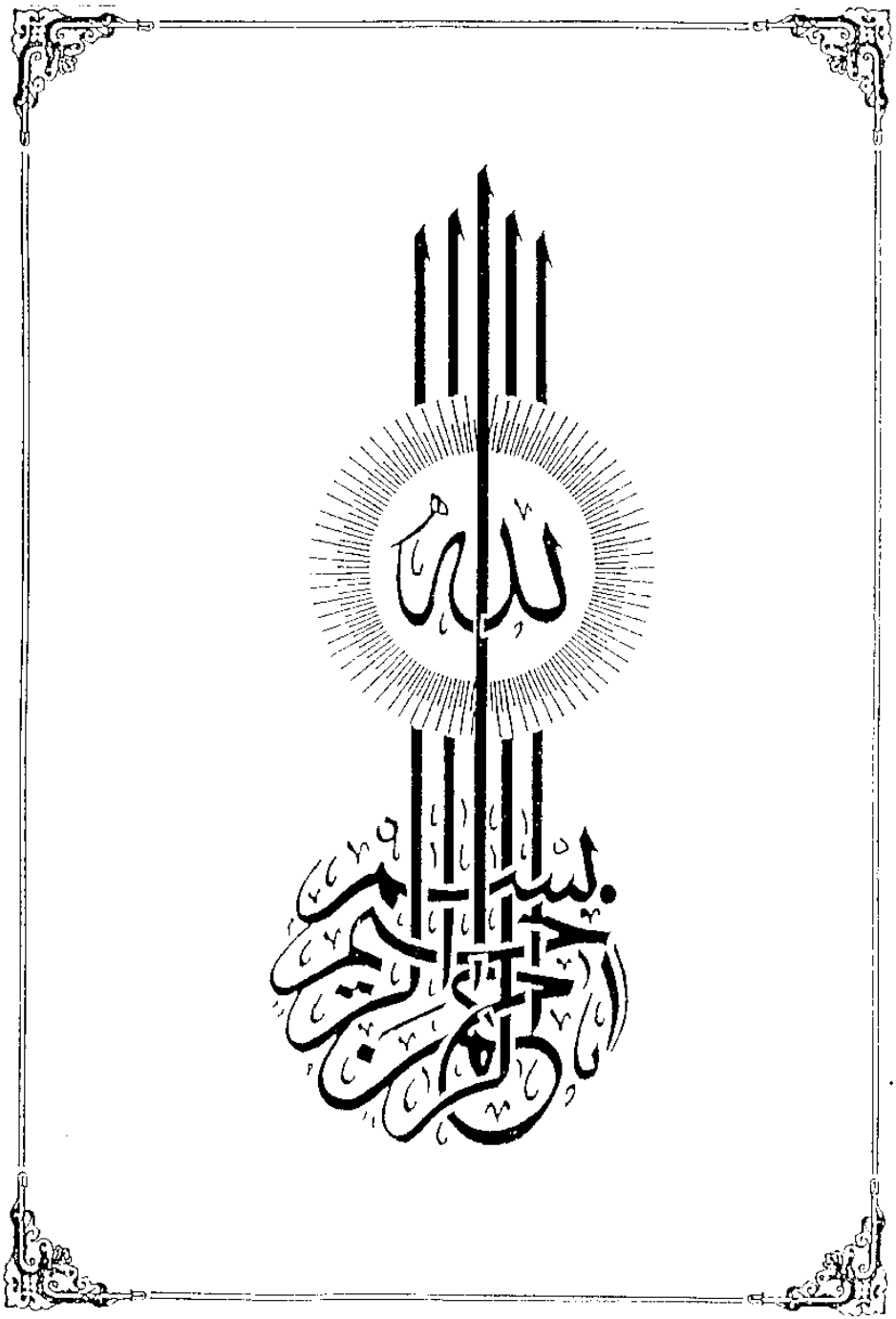
بسم الله الرحمن الرحيم

وأنزل الله عليك الكتاب والحكمة وعلمك ما لم تكن تعلم



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ABBREVIATIONS

AT III	: antithrombin III
a.a	: amino acid.
A p c	: activated protein C.
DIC	: disseminated intravascular coagulation
DVT	: deep venous thrombosis
EIA	: enzyme immunoassay
ElISA	: enzyme linked immunosorbent assay
FDPS	: fibrinogen, fibrin degradation products.
FR-AGS	: fibrin related antigens
Gla-residue	: ɣ -carboxyglutamic acid residues.
HCII	: heparin cofactor II
HMK	: High molecular weight kininogen
M.wt.	: Molecular weight.
PC	: protein c
PAI	: plasminogen activator inhibitor
PA	: plasminogen activator
PCI	: protein c inhibitor
PS	: protein s
RID	: radial immunodiffusion
RIA	: radio immunoassay
TXA_2	: Thromboxane A_2
$V\ III_c$	: antihermophilic factor

$V\ III_{vw}$: Von Willebrand factor

V III R or R.C : ristocetin induced platelet aggregation.

XL fibrin derivatives : X linked fibrin derivatives.

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CONTENTS

INTRODUCTION

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Natural Inhibitors of the Coagulation Enzymes

The rate of intravascular coagulation that occurs under normal physiological conditions are limited by three or more mechanisms:

1- Due to constant flow of blood in the vessels, the local concentrations of coagulation factors remain below levels that promote fibrin formation.

2- The system is also regulated by numerous circulating natural inhibitors of the coagulation enzymes (will be discussed in details).

3- Rapid removal of activated clotting factors, such as X_a, by the liver is another clotting modulatory mechanism (Jones, Peterson, 1984)

Inhibitors of blood coagulation my be:

A- Physiological inhibitors or,

B)- Pathological inhibitors.

A) Physiological Inhibitors:

1- Antithrombins,

2- Protien c and its potentiator protien S,

3- α_2 macroglobulin,

4- α_1 antitrypsin,

5- C_1 estrase inhibitor.

(all these will be discussed latter on in details).

6- Prostacyclin:- which is a powerful inhibitor of platelet aggregation and is released by the action of intimal prostacyclin synthetase on prostacyclin endoperoxidase (Weiss, 1975).

7- Heparin:

It is a sulphated polysaccharide. It is the strongest organic acid synthesized in the body and in solution carries a strong electro-negative charge (Laurence and Bennett, 1980). It is produced by most cells which are distributed typically around small vessels and capillaries in most tissues (Ganong, 1981) and is demonstrated in extremely small quantities in circulating blood (Sharnoff, 1980).

It increase the negativity of the vessel wall and this inhibits thrombus deposition (Ganong, 1981), inhibits the activation of factor IX and markedly increase the rate of inactivation of factor X by antithrombin III (Woodlif and Herrmann, 1979), and aids adsorption of thrombin on fibrin threads and inhibits the autocatalytic action of the thrombin as well as the action of fibrinogen (Ganong, 1981).

In spite of this wide spectrum of activity it has not been proved that heparin has any physiologic role in maintaining blood in the fluid state (Ganong, 1981).

B)- Pathological Inhibitors:

Pathological inhibitors of coagulation are acquired inhibitors which are also described as "circulating anticoagulants". These inhibitors may

develop in patients with congenital deficiency in one factor, after multiple transfusions or in patients with previously normal haemostasis. In this last group, anticoagulants may be directed against one specific factor, or against plateletes, or in other instances, interfere with a phase of coagulation. They are observed in various clinical conditions but frequently common in systemic lupus erythromatosis. Bleeding is common if a single factor e.g. factor VIII or IX is involved but is very rare when a phase of coagulation is inhibited, moreover thrombosis is often observed in these situations (Hougie, 1977).

Antithrombin V and VI are pathological inhibitors. Antithrombin V has been observed in rhomatoid arthritis (Loeliger and Hers, 1957) and in myeloma (Verstraete and Vermylen 1959).

The aim of work:

The aim of this work is to supply a comprehensive review about this natural inhibitors. This will be a beneficial aid for postgraduate investigators interested in this field.

PHYSIOLOGY OF HAEMOSTASIS

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Haemostasis may be defind as spontaneous arrest of bleeding from ruptured blood vessels. In man, haemostasis is achieved by a highly integrated process involving the blood vessels, the blood platelets and a number of plasma proteins which participate in the coagulation and the fibrinolytic pathways. If any of these component is disordered, haemostasis fails.

A) Role of blood vessels:

The normal vascular response to trauma is vasoconstriction in an attempt to shunt blood away from the area of damage (Jaffe, 1983). This is mediated at first by a local axon reflex and then maintained by the action of serotonin released from the platelets (Rand and Reid, 1951).

Prostacyclin (prostaglandin I_2), an inhibitor of platelet aggregation in vascular tissues was detected, suggesting that the blood vesseles possess a mechanism for actively retarding platelet deposition on their walls (Moncada, et al. 1976). Also platelet contain adrenaline (Markwardt, 1967) which would contribute to vascular constriction particularly that of the arterioles.

Moreover, the vasoactive peptides of the kinin system seem to cause vasoditation and increased permeability resulting in oedema and loos of plasma from the vessels, with red cell packing leading to stasis: This response does not result in haemostasis but assists the haemostatic process in small vessels (Zucker, 1947).

Moreover, both AT III and plasminogen activator have been identified in endothelial cells especially in veins and release of the latter into the blood stream following venous occlusssion can readily demonstrated (Hoffbrand and Lewis, 1972).

Von Willebrand factor (VIII: VWF) is also synthesis by the endothelial cells of blood vessels and this factor is involved in the adhesion of platelets to subendothelium as it can bind to collagen and platelets contain a surface receptor for it (Bolhuis et al., 1981).

B) Role of platelets:

Electron microscopic studies of platelet morphology and the sequence of reactions that follow injury of vessel wall have revealed the role played by the platelet during haemostasis. This can be summarized as follows: (Barnhart , Lusher, 1981)

1- Adhesion of platelets to the injured vessel wall

2- The platelet release reaction.

3- Platelet aggregation.

1- Platelet Adhesion

Platelets do not adhere to normal endothelial cells but do adhere to gaps between these cells (Born G.V.R. et al., 1984).

Following blood vessel injury, platelet adhere to the exposed sub-endothelial connective tissues. (Weiss, 1975) including collagen and microfibrils, mediated by factor VIII Von Willebrand factor (Zimmerman et al., 1983)

and probably fibronectin which mediates a variety of cell adhesion phenomenon (Mosher, 1980) as heparin hyaluronic acid and fibrin.

2, 3 Platelet aggregation release

After adhesion of a single layer of platelets to the damaged vascular endothelium, certain substances initiate platelet aggregation. These substances include exposedcollagen fibres, ADP, adrenaline, serotonin, thrombin and certain arachidonic acid metabolites, itcluding thromboxane A_2 (TXA_2) (Born et al., 1976).

Human platelet aggregation may occur by at least two or three independent but related pathways. The first pathway of activation entails arachidonic acid metabolism. Activation of phospholipase enzyme releases free arachidonic acid from the membrane phospholipids (Marcus, 1981), 50% of arachidonic acid is converted by the enzyme cycloxygenase into the cyclic endoperoxides PGG_2 and PGH_2. Most of the endoperoxides are then rapidly converted by the thromboxane synthetase enzyme complex into TXA_2 which cause platelet granules release, local vasoconstriction and after release stimulates other platelets to aggregate locally (Yardumian et al., 1986).

The second pathway of platelet activation depends on various platelet activators including thrombin and collagen producing an increase in the amount of free cytoplasmic calcium to cause directly the release reaction (White, 1980).