STUDIES ON THE EFFECTS OF GLUCOCORTICOID HORMONES ON FIBRINOLYSIS

THESIS

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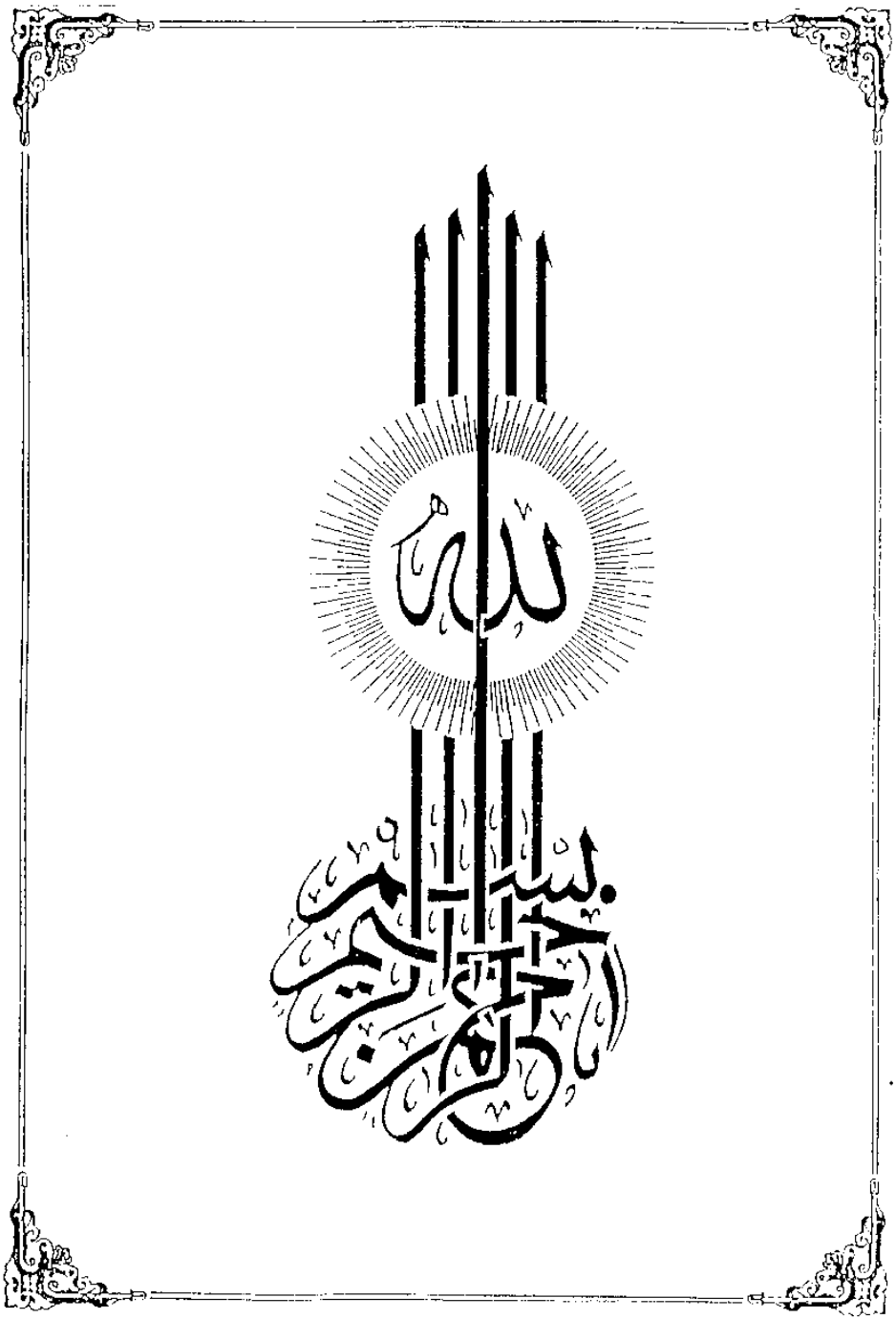
بسم الله الرحمن الرحيم

وقل رب زدني علما

" صدق الله العظيم "



A C K N O W L E D G M E N T

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C O N T E N T S

INTRODUCTION

The body is constantly being challenged by a multiplicity of noxious stimuli which require a well-developed defence mechanism to ensure survival, but these mechanisms may also become hostile to the organism and lead to disease.

The haemostatic mechanism is the best established, and it guards against unnecessary blood loss after trauma. Kallikrein / kinin system provides leukotactic and vasoactive components. The complement system provides chemotactic, phagocytic-promoting and lytic activities against infections and immune diseases. The fibrinolytic system, the fourth one of these plasma systems, protects against thrombosis. In addition, it has another function that may be more important than its intravascular role, that it keeps the tissues clear of unwanted protein such as fibrin(Browse, 1978).

In fact fibrin formation and deposition is not limited to intravascular thrombosis, but it is also an integral part of tissue inflammatory response to any injury. It can be fairly stated that the rate of deposition of fibrin as well as the physical, chemical and morphological characteristics of deposited fibrin determines the natural history of a wide

variety of pathological processes in man. An enzyme system capable of hydrolyzing fibrin and removing fibrin deposits intravascularly or extravascularly seems desirable as an essential physiological defence mechanism (Bang, 1971).

That the adrenal gland is closely concerned with the ability of the organism to resist noxious stimuli has been known for a very long time. The adrenal response is aroused by almost any threat to the body equilibrium or homeostasis. It is now well established that the adrenal cortical hormone, hydrocortisone, is closely related to protection of the body against stresses, and , as well , has a great influence on the mechanism of both inflammation and immunity. In fact, glucocorticoids are widely used in clinical practice in the treatment of a diversity of diseases, especially those in which inflammatory or immunological phenomena are believed to play a predominant role. Despite this, little is known about the precise effect and mechanism of action of glucocorticoids on fibrinolysis.

It is, therefore, worthwhile to further investigate the effect of glucocorticoids on the fibrinolytic activity after the methods for its measurement have been simplified.

Even more pressing, it may help to introduce a new thrombolytic agent for prolonged administration.

REVIEW

OF

LITERATURE

HISTORICAL ASPECTS

The fact that human blood posses fibrinolytic activity has been known for many years. In 1794, Hunter recorded that in animals killed by lighting or electricity or in animals who are run very hard and killed in such a state, the blood does not clot. This phenomenon was partially explained by Morawitz(1906) who noted that the blood from victims of sudden death contained no fibrinogen and could destroy the firbrinogen and fibrin of normal blood.

Denis (1838) observed that the blood clots obtained in wet cupping redissolved in less than 24 hours, and Green (1887) noted that fibrin prepared from ox blood and dissolved when the blood in saline, and it could not be clotted again by thrombin. Few years later, Lustre (1895) during a course of phlebetomy in dogs observed a reduction of fibrin which he attributed to its destruction by a process which he named "fibrinolysis". In 1903, Hedin could detect spontaneous fibrinolytic activity in the globulin fraction of ox blood.

The main outline of present knowledge of spontaneous fibrinolytic activity in blood was finally obtained by Macfarlane (1937) who showed that in man fibrinolytic activity

in blood can be provided by surgical operation.

From the last decade of the nineteenth century, knowledge was accumulating on methods by which lytic activity might be induced. In (1889) Denys and Marbaix found that treatment of serum with chloroform induced proteolytic and fibrinolytic activity. Delezenne and Pozerski(1903) showed that the action of chloroform was probably to remove inhibitors of fibrinolysis. Opie and Berker (1907) found that as with spontaneous activity the fibrinolysis induced by chloroform treatment of serum was in the globulin fraction.

Wolf (1908) induced fibrinolytic activity in dogs by injection of peptone and thought that lysis of blood clots was the end result of the coagulation process, and that coagulation was due to the activity of proteolytic enzymes.

Tillett and Garner in (1933) made a fundamental advance in knowledge of the fibrinolytic mechanism. They found that the culture medium of certain strains of haemolytic streptococci contained a substance capable of producing rapid lysis of human blood clots (now named streptokinase). Milstone (1941) showed that this streptococcal product did not lyse highly purified human fibrin, but if a small quantity of the euglobulin fraction of human serum was added, lysis

occurred quickly. Christensen (1945) found that the euglobulin fraction of human serum owed this effect to its content of inactive substance (now named plasminogen) which is converted to the active proteolytic enzyme (plasmin) by a variety of activators, of which streptokinase is one.

The terms plasminogen and plasmin were suggested by Christensen and McLeod (1945).

COMPONENTS OF THE FIBRINOLYTIC SYSTEM

1) Plasminogen (Profibrinolysis):

It is a single chain beta globulin that is precipitated out in the euglobulin fraction of plasma (Milstone, 1941) and of a molecular weight of 83,000 (Davis & Englert, 1960) to 93,000 (Cleyy's & Vermylen, 1974).

Activation of this zymogen to plasmin is a proteolytic process similar to formation of other proteolytic enzymes from their inactive precursors as trypsin and thrombin(Thorsjaersig et al, 1958).

The sequence of amino acids in the plasminogen molecule has been elucidated recently and data show three distinct regions, a kringle region containing lysine binding sites that are involved in the adsorption of plasminogen to fibrin, C-terminal region containing serine residue that is essential for the enzyme activity and a N-terminal part. Ichinose & Summaria (1971) found that the activators split specific arginyl bonds resulting in uncovering of the active sites with formation of the two-chained plasmin molecule.

The structure of plasminogen observed in the electron microscope is generally circle shaped with a diameter varying between 6 - 7.5 nm. This plasminogen structure manifests