SUPRARENAL FUNCTION IN SOME PHYSIOLOGICAL AND PATHOLOGICAL CONDITIONS

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THESIS

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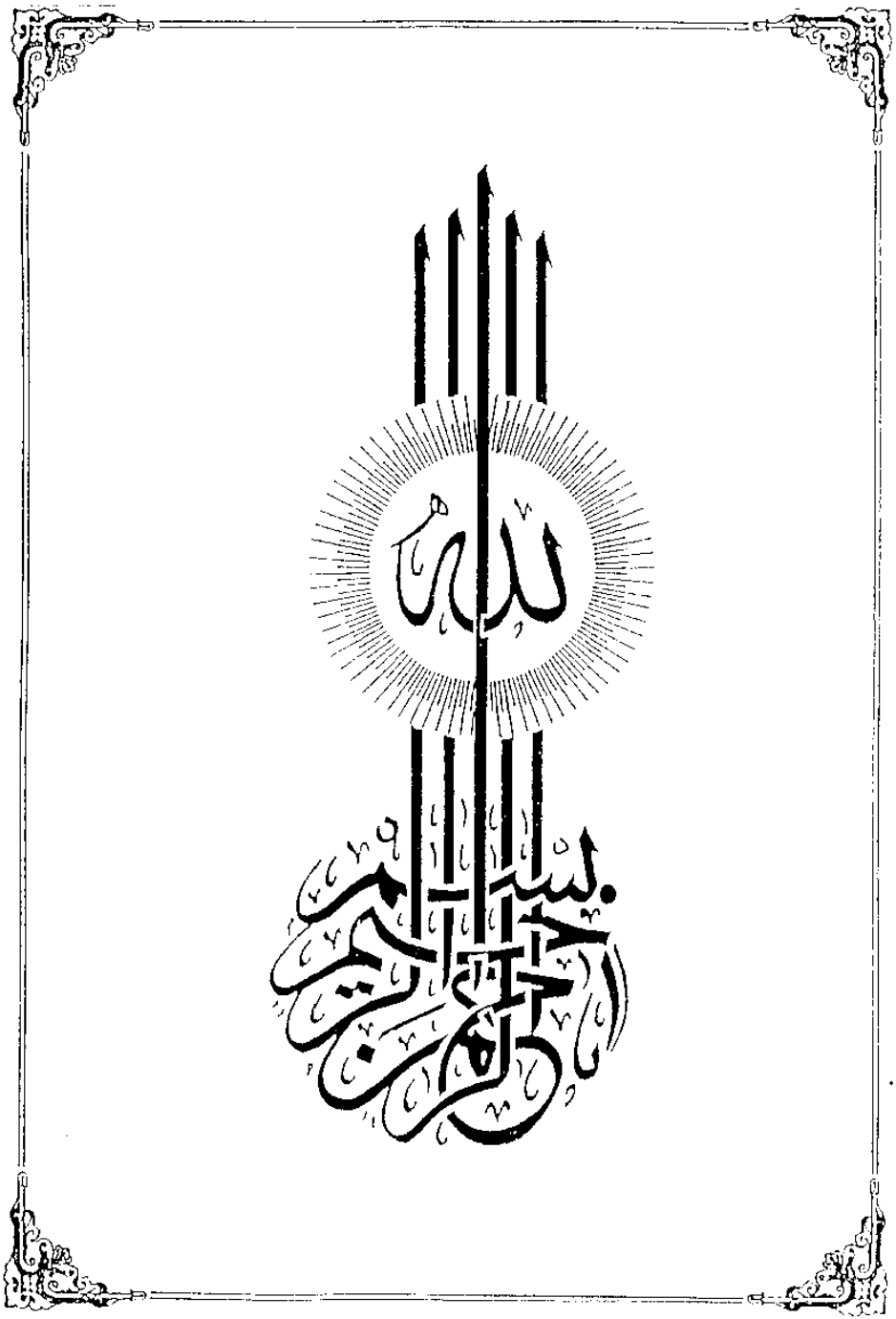


C O N T E N T S

AIM OF THE WORK

The liver is one of the important regulators of adrenocortical function. The normal liver inactivates the adrenocortical hormones; 17-ketosteroids and hydroxycorticoids output, are therefore reduced in liver disease.

Bilharziasis is an endemic disease in Egypt. This disease affects, to a great extent, the metabolic functions of liver. Abdel-Aziz et al. (1976-a) showed a highly significant decrease in both urinary 17-ketosteroids and 17-ketogenic steroids in bilharzial liver cirrhotic cases. It has been reported that undernutrition in such bilharzial cases produces a condition of pseudo-hypophysectomy (Abdel-Kader et al., 1973).

The functional significance of the proximity of the sources of epinephrine and cortisol is of interest. Recent studies show that blood flows through numerous channels from cortex to the medulla (Johnston, 1973) suggesting that cortisol is important in the conversion of norepinephrine to epinephrine, and provided the evidence of synergism between cortisol and epinephrine in peripheral tissue. Norepinephrine is the major catecholamine produced in foetal life (Zuspan et al.,1967).

In the neonatal period and afterwards the proportion of epinephrine secreted increases gradually until it becomes the major catecholamine.

The aim of the thesis is to study the suprarenal function (both cortex and medulla) in normal physiological cases and those affected by Bilharziasis, to show if there is any defect of a primary or secondary origin.

REVIEW OF LITERATURE

I- ANATOMY OF THE SUPRARENAL GLANDS

The suprarenal glands are composed of two types of tissues. The central portion (the medulla) and the outer portion (the cortex), which is essential to life.

The embryologic origin of the adrenal cortex is quite different from that of the adrenal medulla. The hormones of the adrenal cortex are steroid derivatives, they include gluco-corticoids, mineralocorticoids and sex hormones.

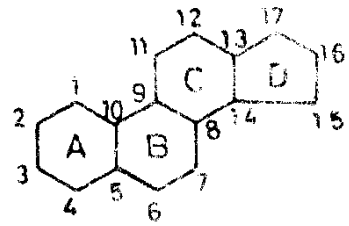
The hormones of adrenal medulla are epinephrine (adrenaline) and norepinephrine (noradrenaline) which are related to the catecholamines. The adrenal medulla is not essential to life. Indeed, the medulla releases very little secretion into the circulation under resting conditions, probably too little to have any physiological consequences. In situation of acute stress the medulla discharges much larger amounts of catecholamines, the secretion of which has metabolic consequences, circulatory and other effects as well.

There is evidence for the presence of two types of chromaffin cells, one containing norepinephrine and the other contain epinephrine (Eranko, 1960), these cells may be innervated differently, and the secretion of norepinephrine, and of epinephrine may be specifically controlled in some species.

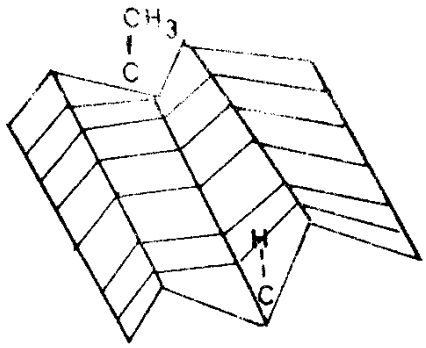
II- CHEMISTRY OF THE ADRENAL STEROIDS

Rogoff and Stewart (1937) were the first to demonstrate adequate adrenal replacement therapy in the completely adrenalectomized dog by injection of aqueous extracts of adrenal tissue (Thorn, 1972). During 1937 several groups of investigators, notably Kendall and Phiffer, isolated from adrenal extracts crystalline compounds with adrenocortical activity (White et al., 1964-a). Since then, marked advances in the chemistry and pharmacology of the adrenal steroids came to light.

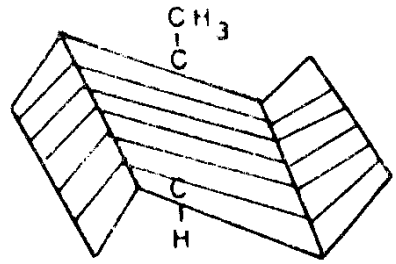
All the known hormones of the adrenal cortex are of steroid in nature. Each ring can be joined to the other in two ways producing a cis or trans isomers about



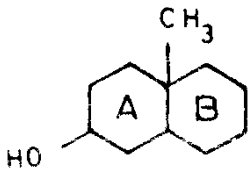
Cyclopentanoperhydrophenanthrene ring

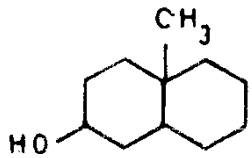


Cis



Trans (ALLO)





Diagrammatic representation of steroisomersim of the steroid molecule.

the ring junction. In the naturally occurring steroid hormones, however, only isomerism about the A-B ring junction has been observed; the B-C, and C-D ring junction are always trans. i.e. the steroid hormones can only occur in two isomeric forms depending on the isomerism about the A-B junction (Makin et al., 1972). The natural steroids possess a Δ-4-3-one group and an alphaketol side chain at C_{17}. Only aldosterone possess and aldehyde group at C_{18}. An oxygen substituent at C_{11} is a characteristic of the glucocorticoids, and cortisol appears to owe its physiological activity largely to the presence of a hydroxyl group in this position. The reduction of an 11-oxo group to an 11-hydroxyl group seems essential for glucocorticosteroids activity and is dependent on the sterochemistry of the (A)and(B)rings (Bush, 1956; Bush and Mabesh, 1959).

Three structural features are essential for all known biological actions of the natural adrenocortical hormones :

1- Double bond at $C_4 - C_5$.

2- Ketonic group at C_3.

3- Ketonic group at C_{20}.

Certain additional structural features have a profound effect upon the biological activity of these compounds :

(1) A hydroxyl group at C_{21} enhances sodium retention and is necessary for activity in carbohydrate metabolism.

(2) The presence of O either as, OH or as Ketone at C_{11} is necessary for carbohydrate activity and decreases sodium retention.

(3) A hydroxyl group at C_{17} increase carbohydrate activity.

On the basis of these relationships between structure and biological activity, the adrenal cortical hormones may be classified into three categories :

(A) Those possessing O at C_{11} (either OH or Ketone) with activity in carbohydrate and protein metabolism and relatively minor effect on electrolyte and water metabolism. These have been referred to as the 11-oxygenated corticosteroids or 11-oxysteroids and include; corticosterone (Compound B), 11-dehydrocorticosterone- (Compound A), 11-dehydro-17-hydroxycorticosterone (Compound E, cortisone) and 17-hydroxycorticosterone (Compound F; hydrocortisone, cortisol).

(B) Those without O at C_{11} with virtually no activity in carbohydrate or protein metabolism and major effect on electrolyte and water metabolism. The most important representatives of this group are 11-deoxycorticosterone and 17-hydroxy-11-deoxycorticosterone (Compound S).

(C) Aldosterone which in solution, exists in two tautomeric forms, with hemiacetal and aldehyde structure, respectively. This differs from the other corticoids in that the usual methyl group at C_{18} is replaced by an aldehyde group. Approximately 30 crystalline steroids have been isolated from extracts of adrenal gland, they are :

1) C_{19} steroids: having androgenic activities.

2) C_{21} steroids: having a mineralocorticoid or glucocorticoid activities.

3) C_{18}: estrogens.

Many of the steroids isolated from adrenal cortex are intracellular intermediates, only few steroids have been shown to be normally secreted into the blood stream, the main ones being: cortisol, corticosterone, aldosterone, dehydroepiandrosterone, androstenedione and 11-B-hydroxy-androstenedione, (Makin et al., 1972).

III- BIOSYNTHESIS OF ADRENOCORTICAL HORMONES

The major precursor of all steroid hormones is the cholesterol; endogenously synthesized via the acetate pathway, and to a lesser extent that derived from the diet (Gill, 1972). The cholesterol is converted to pregnenolone by scission of the side chain between C_{20} and C_{22} by means of a desmolase enzyme. The process requires NADPH and molecular oxygen (White et al., 1964-b), 20 α-hydroxy-cholesterol and 20 α-22-hydroxycholesterol being intermediates, pregnenolone formed is then converted to the various steroids.