EFFECT OF ANDROGENS ON THE SUPRARENAL GLAND AND ISLETS OF LANGERHANS IN THE RAT.

THESIS

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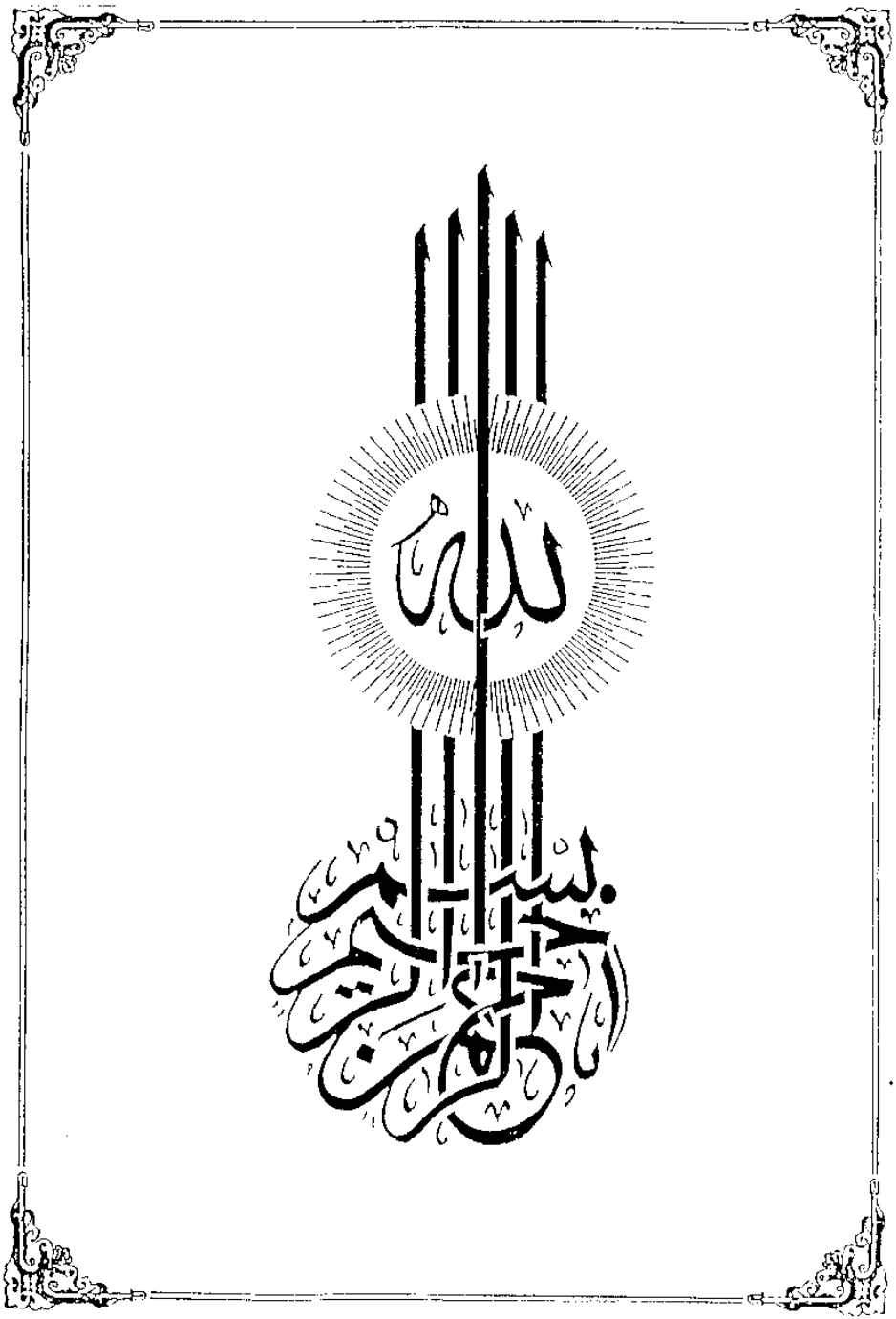

Aim of Work

The effect of androgens on the histology of suprarenal gland and islets of Langerhans have not been fully investigated. In this experiment we aim to study the affect of one of the commercially used androgens (dehydroepiandrosterone) which is used in treatment of many physical and psychological disturbanoes.

INTRODUCTION

I N T R O D U C T I O N

I- Sources of Androgens

Dorfman and Shipley (1956) said that, the presence of androgens in the testis, the ovary and adrenal cortex has been established.

Claims have also been made that androgens are present in the placenta, the epididymis and the anterior pituitary.

Testis

There is evidence that this hormone is produced by the interstitial glandular tissue. If the seminal epithelium is caused to atrophy without damage of the interstitial tissue, androgenic material continues to be secreted by the modified testis. Such a condition is realized if an animal is made cryptorchid or the testes are irradiated with adequate dosage of x-ray or radium. In spite of the destruction of the seminal epithelium in the cryptor-chid testis, the accessory genital organs are preserved in a normal functional state due to continued androgen secretion. Administration of pitch to rodents causes damage of the testicular interstitial tissue with a parallel atrophy of the secondary sex glands, while the seminal epithelium remained normal.

Ovary

No pure androgen has yet been isolated from ovarian tissue, although it is possible to demonstrate androgenic material in extracts prepared from this gland. From evidence in mammals and birds there appears to be little doubt that the ovary elaborates an androgenic secretion. The administration of gonadotrophic hormone to the pullet causes stimulation of the ovary with the simultaneous stimulation of the comb. All evidence available indicates that comb growth in the fowl can not be stimulated by oestrogens but only by androgens.

Furthermore, if gonadotrophic hormone is administrated to ovariectomized chicks, the combs are unaffected. The effect therefore appears to be through the ovary which has been stimulated to secrete androgens by the administration of trophic hormone.

Adrenal cortex

Androgens have been isolated from adrenal cortex by direct chemical extraction. Indirect evidence of their elaboration by this gland includes the high concentration of urinary androgens in certain patients with adrenocortical hyperplasia or tumour, the decreased concentration in conditions

of adrenocortical hypofunction and the persistence of substantial quantities of androgen in the urine if the glands are removed.

In cases of adrenal hyperplasia and tumors in women and in children of both sexes, masculinization is usually present. This itself, is a biological indication that abnormal amounts of androgens are available. In addition, from the urines of such individuals large amounts of androgens have been isolated. Values as high as one hundred times the normal concentration have been found.

The administration of crude adrenocorticotrophic hormone to castrated rats promotes regrowth of the prostate and seminal vesicles but no such effect is obtained in adrenalectomized animals.

Plant Sources

Androgenic material has been identified in wheat germ oil. The activity was detected by means of its action the chicks comb and by the ability of the material to stimulate the seminal vesicles of castrated rats.

II- Biochemistry of Androgens

Standerd unit of activity

Harper et al (1977) said that androsterone is used as the international standard of androgen activity.

One IU = 0.1 mg of androsterone.
Although this hormone does not occur in the testes, it is excreted in the urine of males as a metabolite of testosterone.

Biosynthesis

Harper et al (1977) said that the principle male hormone, testosterone, is synthesized by the interstitial (leydig) cells of the testes from cholesterol through prgnenolone, progesterone and hydroxyprogesterone which in then converted to the C-19 ketosteroid, androstenedione, the immediate precursor of testosterone. Alternatively, the pathway through hydroxypregnenolone and dehydroephiandrosterone can be used to produce androstenedione. A direct conversion of dehydroepiandrosterone to testosterone has been established in which androstenedione is by passed, Dehydroppiandrosterone in this way is initially reduced to it's 17 - hydroxy derivatives which are then converted to testosterone. These reaction

are also a part of the biosynthetic pathway in the adrenal for the formation of the androgenic (C-19) steroids. In addition to testosterone, the androstenedione and dehydroepiandrosterone (androgens also produced by adrenals) are synthesized in the testes, although in amounts and with total androgenic potency far less than that of testosterone.

Testosterone is converted by the enzyme 5a reductase in some but not all target tissues to the more potent dihydrotestosterone, which in adults is the active intracellular androgen. As, with other steroids, the androgens may initially bind to a specific cytosol receptor protein. The complex inturn is transported to the nucleus where it interacts with chromatin triggering RNA & protein synthesis.

In general, the testes and the adrenals have similar qualitative capacities to synthesize androgens. Since the testes lack 11 - hydroxylase activity, however, only the adrenals can syntheize the glucocorticoid and mineralocorticoids. The principle metabolites of testosterone are androsterone and etiocholanolone.

III- General meehanism of action of hormones

Harper et al (1977) mentioned that although the exact site of action of any hormone is still not established, 5 general sites have been proposed:.

(A) Induction of enzyme synthesis at nuclear level.

Steroids may act to stimulate RNA production in the target cell nucleus and there by increase the synthesis of a specific enzyme or group of enzymes catalyzing a specific metabolic pathway. Steroid hormones initially act by binding to a specific high affinity receptor protein in the cytosol. The complex that is formed is then transported to the nucleus of the cell wherein it reacts with the nuclear chromatin. This combination inturn influences the synthesis of messenger RNA (m RNA) that will act as a template directing the synthesis of specific protein enzymes. Changes in metabolism are produced by this indirect route. It is to be noted that a direct chemical reaction of the hormone with DNA or RNA poly-nucleotide is not likely to occur. Instead, it is postulated that the hormone must first combine with a specific receptor protein and it is this combination that acts on DNA chromatin.

(B) Stimulation of enzyme synthesis at ribosomal level.

Activity is at the level of translation of information carried by the messenger RNA on to the ribosomes.

(C) Direct activation at enzyme level

Treatment of the intact animal or of isolated tissue with some hormones results in a change of enzyme activity not related to denovo synthesis, these hormonal effects are usually extremely rapid.

(D) Hormonal action at the membrane level.

Many hormones seem specifically involved in the transport of a variety of substances across cell membranes including carbohydrates, cations, amino acids and nucleotides.

Most protein hormones and catecholamines activate different membrane enzyme systems by direct binding to specific receptors on the cell membrane rather than in the cytosol.

(E) Hormonal action in relation to the level of cyclic nucleotides.

The hormones probably act at specific receptor sites in the different cell membranes which inturn activate adenylate

cyclase. It is probable that receptors for different hormones in a cell membrane activate a relatively common adenylate cyclase. Most of varied effects of cAMP appear to reflect its general ability to activate a large variety of phosphokinase enzymes thus cAMP activation of phosphorylase is the result of a specific activation of the enzyme phosphorylase kinase which result ultimately in the conversion of inactive dephosphophosphorylase to active phosphorylase.

IV- EFFECT OF ADRENAL ANDROGENS

Ganong (1977) pointed out that androgens are the hormones that exert masculinizing effects and they promote protein anabolism and growth. Testosterone from the testes is the most active androgen and the adrenal androgens have less than 20 % of its activity.

Secretion of the adrenal androgens is controlled by ACTH, not by gonadotropin. The amount of adrenal androgens secreted is almost as great in castrated males and females as in normal males, so it is clear that they exert no significant masculinizing effect when secreted in normal amounts.

In adult males, excess adrenal androgen secretion merely accentuates existing characteristics but in prepuberal boys, it causes precocious development of the secondary sex characteristics without testicular growth (precocious pseudopuberty). In prepuberal and adult females it causes masculinization which when marked produces the striking clinical picture of (adreno genital syndrome).

V- Action of Androgens

Ganong (1977) stated that testosterons and other androgens exert a feed back inhibitory effect on pituitary L.H. secretion, they cause development and maintenance of the male secondary sex characteristics and exert an important protein anabolic growth promoting effect.

Along with FSH, testosterone is responsible for the maintenance of gametogenesis.

Effect on secondary sexual characteristics

The widespread changes in hair distribution, body configuration and the genital size that develop in boys at puberty and the male secondary sex characteristics are summarized as follows:.

Penis increases in length and width, scrotum becomes pigmented and rugose, Seminal vesicles enlarge and secrete and begin to form fructose. Prostate and bulbo-urethral glands enlarge and secrete, larynx enlarges, vocal cords increase in length and thickness and voice becomes deeper. Beard appears. Hair line on scalp recedes anteriorly. Pubic hair grows with male (triangle with apex up) pattern hair appears in axillas, on chest and