ABSTRACT. There is increasing evidence that androgen therapy in men may be effectively applied in several conditions to improve well being and health. Classical indications for androgen therapy in males are represented by primary or secondary hypogonadism, delayed puberty, aplastic anemia and that secondary to chronic renal failure, protein wasting diseases such as trauma, burns, tumors and infectious diseases. Androgen innovating applications in men are represented by aging and visceral obesity associated with the metabolic syndrome. In addition, it is clear that appropriate testosterone treatment can be adequately used in male contraception, provided spermatogenesis is abolished and tolerability is adequate. Due to unphysiological hormone levels achieved by currently available testosterone preparations, new delivery systems have been produced to achieve more physiological and sustained hormone levels and improve tolerability and action at the levels of target tissues. Some of them are now available in several countries and new formulas are under development.

INTRODUCTION

In the past androgen employment in clinical practice was impeded for a long time because testosterone (T), the principal androgen secreted by the testes, could not be administered efficaciously either by mouth or by parental administration due to its fast degradation. It was therefore necessary both to modify the molecule in order to alter its metabolism and to devise new ways of administration in order to obtain and sustain effective T levels in the blood (1). Classically androgens are used in treatment of male hypogonadism, anemia secondary to chronic renal failure, aplastic anemia, and protein wasting diseases, such as tumors, burns, traumas, AIDS, etc. In the last few years androgen use has increased especially by athletes, aging men and fertile men for hormonal contraception, inducing many researchers to further investigate the principal mechanisms of the action of steroids, the risks and benefits of androgen use and new preparations for therapeutic use. In fact, when a drug is administered, knowing the potential risks and whether the benefits are higher than the side effects becomes essential. Some androgen side effects are the consequence of their physiologic action on target tissues, whereas others may be the results of the toxic effects of molecules modified (1).

In this review we briefly describe all the principal aspects of T physiology, its use in classical conditions such as hypogonadism and new therapeutic perspectives in aging, visceral obesity associated with metabolic syndrome and male contraception. In addition we will describe all old and new pharmacological formulations either available now or to be developed in the near future, with particular emphasis on principal pharmacological aspects, biological action and safety.

PHYSIOLOGY

The hypothalamus produces gonadotropin releasing hormone (GnRH), which in turn stimulates the pituitary gland to secrete luteinizing hormone (LH) and follicle stimulating hormone (FSH). In men LH induces Leyding cells to produce T. FSH acts on
Sertoli cells thereby stimulating spermatogenesis (2, 3). The testicles exert an inhibitory control on LH secretion through sexual steroids (T and estradiol-E2) and on FSH through both sexual steroids (T and E2) and peptides (inhibin B). It is suspected that inhibin B is produced by Sertoli cells under the control of FSH (4). T also potentiates the inhibitory effect of the opioids on GnRH. Approximately 7 mg of T is produced daily in normal weight men (5). T can act either directly on target cells or it can be converted to dihydrotestosterone (DHT) by the 5α-reductase enzyme or to E2 by the aromatase enzyme complex. The 5α-reductase enzymes are most abundant in the prostate gland, in the skin and in the reproductive tissues. On the contrary, the aromatase enzyme complex is most abundant in the adipose tissue, in the liver and in the central nervous system nuclei (6). Both T and DHT link androgen receptors but, since DHT has more affinity for specific receptors, it is more powerful than T (5).

The mechanism of action of T and other steroid hormones is well known. Endogenous and exogenous steroids circulating in the blood system cross the cellular wall of target cells and then bind specific cytoplasmatic receptors with a high specificity and a relatively low affinity. The hormone-receptor complex then moves into the nucleus and binds to a specific nuclear chromatin site, stimulating mRNA transcription and then specific protein translation. Inherited abnormalities of androgen receptors (to date ten different mutations have been identified) change tissue sensitivity to these hormones and lead to different pathologic conditions (7).

**ANDROGEN BIOLOGICAL EFFECTS**

**Skin and hair**

Sebum production is an androgen-dependent process and DHT is believed to be the most active hormone in sebaceous glands (6). Even if numerous studies have demonstrated a positive correlation between acne entity and androgen serum levels, including DHT, most subjects of both sexes with severe acne do not have elevated serum androgen concentrations. In these cases it is believed that local conversion of precursors may increase androgen concentration in the skin. Androgens, particularly DHT, also control hair follicle development; on some follicles, they induce an extension of the anagen phase (growth phase) with formation of long, thick and pigmented hairs (terminal hair); on other follicles (for example scalp) they induce the formation of fine, short and non-pigmented hairs. Axillary and lower pubic hairs respond to low concentrations of androgen and then they are present in both sexes. Hairs on the face, chest and upper pubic area require high blood concentrations of androgen and therefore they are typical of the male sex. Most men and a lot of women with genetic predisposition have androgenic alopecia. Many studies suggest that balding arises from an accumulation of DHT in the relative follicles. In fact DHT inhibits metabolism of hair follicles. It has also been demonstrated that there are high 5α-reductase enzyme levels in the scalp (6).

**Liver**

Androgens induce hepatic synthesis of clotting factors, triglyceride lipase, sialic acid, α1-antitrypsin and haptoglobin (8). Conversely, androgens decrease the production of several proteins, including sex-hormone binding globulin (SHBG), cortisol binding globulin (CBG), thyroxine-binding globulin (TBG), transferrin and fibrinogen.

**Lipids and lipoproteins**

In men hormonal regulation of the lipid metabolism is complex and not completely known but, as in women, sexual steroids appear to be key regulator factors acting on lipid secretion and catabolism (9). Men generally have lower plasma concentrations of high-density lipoprotein (HDL) and higher concentrations of triglyceride, low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) than premenopausal women (10). Androgens administered at high doses decrease plasma HDL concentrations (11, 12), probably by increasing their catabolism. Sexual differences were documented in two enzymes implicated in HDL metabolism, namely lipoprotein lipase (LPL), which is higher in women than in men and hepatic lipase (HL), which conversely is higher in men. HL is stimulated by androgens and inhibited by estrogens. HL is the main enzyme responsible for HDL clearance in humans (10).

**Reproductive tissues**

Androgens stimulate prenatal differentiation and pubertal development of the testes, penis, epididymis, seminal vesicles and prostate gland (6). In adults, androgens are required for the normal trophic and functional maintenance of these tissues. T is also a potent stimulator of spermatogenesis acting on spermatogonial population and on spermatid maturation (13, 14). T acts also on peritubular cells (are myoid cells endowed with the ability to contract that serves to transport released germ cells and possibly to extrude fluid towards the epididymis) and on Sertoli cells within the testes pre-