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AROMATASE INHIBITORS AND PROSTATIC HYPERPLASIA

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Recent findings implicate a shift in the balance between estrogens and androgens, in favour of estrogens, as an important factor in development of benign prostatic hyperplasia in aging men. Inhibitors of estrogen biosynthesis (aromatase inhibitors) might therefore find application in therapy and/or prophylaxis of this condition. 1-Methyl-1,4-androstadien-3,17-dione (SH489) was found to be a potent inhibitor of human placental aromatase in vitro, showing a high affinity for the enzyme (K_i=6x10^{-8} mol/l) and also demonstrating a NADPH-dependent irreversible inhibition. The compound and its principle metabolites show no significant binding to steroid receptors, correlating with the absence of endocrinological activity in animals, with the exception of effects directly attributable to aromatase inhibition. In female rats, SH 489 delays the ovarian cycle and rapidly reduces the high serum estrogen levels induced by treatment with PMSG. Aromatization of testosterone in mature male cynomologous monkeys could also be inhibited. To test our therapeutic principle in an animal model, we have employed prostatic hyperplasia induced in castrated beagle dogs. Androstenedione (3 injections/week, 6-9 months treatment) induced both androgenic (largely epithelial) and estrogenic effects (stimulation of the stroma, especially smooth muscle). Simultaneous treatment with aromatase inhibitor (4-hydroxy-androstenedione or SH 489) nearly abolished the effects of androstenedione. These results strengthen the hypothesis that the androgen/estrogen balance has a marked influence on prostate morphogenesis and suggest that aromatase inhibitors may be useful in treatment of human BPH, a predominantly stromal disease.

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Pharmacology of Antiandrogens

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Principally, antiandrogens affect all androgen-dependent organs and functions as for instance accessory sexual glands, spermatogenesis, skin and skin appendages, libido and potency, male sexual differentiation, longitudinal bone growth and bone maturation.
Pharmacologically, it is important to distinguish between the steroidal antiandrogens of the cyproterone acetate type and the nonsteroidal pure antiandrogens (flutamide, anandrone).
For the clinical use of cyproterone acetate in both men and women the 3 main properties are important: Cyproterone acetate is antiandrogenic, it is a quite potent progestogen and it is antigonadotrophic. This antiandrogen is not androgenic at any dose and is not estrogenic.
Based on pharmacological and biochemical backgrounds cyproterone acetate is used in the following indications: Androgen mediated disorders of the skin such as acne, seborrhaea, hirsutism, alopecia, advanced prostatic carcinoma, precocious puberty and male hypersexuality.
For the treatment of dermatological androgen dependent disorders of the skin in man, a topically active antiandrogen without systemic effects would be desirable. Two topically active antiandrogens are under investigation: 17α-propylmesterolone and Ru 38882.