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Symposium Regulation of Androgen Action, Montreal 1984

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During two days (from 29th June – 1st July 1984) a symposium on *regulation of androgen action* was held in Montreal (Canada). It was a satellite meeting of the VIIth International Congress of Endocrinology in Quebec. This high-level meeting was organized by Dr. Bruchovsky (well known scientist in the field of androgen steroids) in conjunction with the research department of Schering AG in Berlin.

The first session was devoted to mechanisms and regulation. *Mainwaring* gave an overview of the present concepts, pointing out the importance of the nuclear matrix as the site for androgen acceptors and gene-expression and of the recombinant DNA-technique for finding androgen sensitive genes. The newest method for receptor localisation is biotin-steroid conjugation with fluorescein-labelled avidin.

Also very interesting is the EM-study of prostatic epithelial cells after castration and after DES-treatment, the latter having a significant effect on nuclear membrane and nucleolus. This means that DES has an intracellular effect in addition to the deprivation of androgens. *McNeal* underlined the inductive effect of stroma in the evolution of BPH by his beautiful morphologic studies of the prostate. *Bruchovsky* compared 5α-reductase and dehydrogenase activity in stroma and epithelium from BPH and prostatic carcinoma. 5α-reductase activity is highest in stroma, but it seems that stromal and epithelial enzymes are different forms of isoenzymes. Both forms can be inhibited by DMAA and dinorchol, but the epithelial enzyme is more sensitive to inhibition. The very important role of co-factors in 5α-reductase activity is still far from clarified.

Mobbs gave an overview of the significance of steroid-receptor determination for prostatic cancer and BPH.

Neumann told about the different properties of 2 potent anti-androgens cyproteron-acetate (CPA) and Flutamide (F) resulting from animal experiments. CPA has a potent progestative activity, as well as anti-oestrogenic and anti-ovulatory activity. Under CPA-treatment LH and FSH decrease, while the same increase under F-treatment. This means that F stimulates Leydig cells, while CPA induces atrophy of the same. CPA also inhibits adrenal androgens.

Results of hormonal manipulation of BPH were given by *Geller*. Although after castration DHT-levels are usually <2 ng/g tissue, about 10% have higher levels. After oestrogen treatment more than 10% have higher levels. A combination of megace and low dose oestrogens, however, brought all DHT-levels down. Tamoxifen could block protein synthesis in BPH and had some effect on E_2-receptors but no effect on progesteron-receptors.

This session was concluded by *Coffey and associates* who compared Canine-BPH to human and indicated the usefulness as well as the limitations of the dog model.

Thereafter 4 workshops took place simultaneously on the subjects: prostatic carcinoma and PBH; Acne and Hirsutism; Androgen resistance and molecular regulation. Besides a few papers there was a large number of posters that were discussed in these sessions. The majority of these posters concerned high level research and caused animated discussions, for which ample time was available.

An interesting subject was the possibility of conservative treatment of BPH with an aromatase-inhibitor such as testolactone.

Tunn reported on a trial in which many patients after 8 weeks of treatment could void without residue and had an average of 26% decrease of prostatic volume. It is possible that in the future other aromatase-inhibitors might be even more effective.

The final session dealt with new directions and methods. *French* reported on the prostatein system to study androgen regulation of gene-expression. *Parker* brought the concept of integration of DNA in the genome of cells. As the nuclear RNA is the most affected by androgenes the study of androgen-sensitivity can best be done after transcription of specific (marker) genes, such as interferon. Only very few cells integrate added DNA or interferon in their genome. These cells can then be cloned and subsequently the response to androgens can be measured.

Rennie was able to prepare nuclear matrix, which contains a large number of binding-sites for androgen receptor. 50% of the nuclear androgen receptors reside in the matrix and it seems that matrix binding and transcription are separate ways of function of receptors. He came to the concept of class A receptors that are bound to the matrix and have a high affinity and low capacity, and class B receptors that are not bound to the matrix and have a high capacity. The large number of low affinity binding sites could account for the retention of large amounts of DHT in the nucleus. However, it remains unclear whether this excess DHT could not be linked to the nucleolus.

Gustafsson pointed out that certain carcinogens, such as TCDD are metabolized only in epithelial prostatic cells. He found that prostatein is binding these carcinogens, which then can activate cytochrome P450 in the microsomes. This opens a perspective of non-receptor markers for androgen action.

Probably the most beautiful research was presented by *Cuhna.* He brought so-called wild type TFM epithelial cells together with specific stroma (urogenital tissue mesenchyma) that contained androgen receptors. Thereby the growth of prostate was induced, although the epithelium did not contain AR. It grew in branches, the tips of which were most responsive to androgens. When these tips were separated, they could again grow to prostate induced by urogenital stroma. His conclusion was that a trophic factor from the stroma induces the epithelial growth.

Chapdelaine finally came to the same conclusion on the basis of experiments with explants of dog and human prostates. It is not the sex steriods but a growth promoting factor that stimulates fibroblasts and epithelial cells. The nature of this trophic factor, probably a peptide, still has to be determined.

This concluded a well conducted and extremely stimulating symposium in which clinicians and scientists participated in a friendly atmosphere with lively discussions and with promising future perspectives.