Meeting Report

SECOND SYMPOSIUM ON BIOCHEMICAL ASPECTS OF STEROID RESEARCH

Weimar, Thuringia, GDR, 14–19 September 1981

L. TRÄGER

Zentrum der Biologischen Chemie, Johann Wolfgang Goethe-Universität, Theodor-Stern-Kai 7, Frankfurt/Main, 6000 Frankfurt/M., FRG

Received 21 January 1982

From 14–19 September 1981 more than 150 scientists from over 10 countries discussed several topics concerning clinical applications of steroids, industrial management of steroid production, progress in basic research of steroid action, and modern trends in steroid biochemistry and pharmacology.

The presentations at the Symposium were arranged in the following sessions: (1) sterol biosynthesis and interactions of microorganisms with steroids; (2) steroid transforming enzymes; (3) application of immobilized biocatalysts; (4) central regulation by steroids; (5) biosynthesis and metabolism; (6) mode of action of steroids. Especially the poster presentations covered clinical and pharmaceutical aspects of sterols and steroids.

C. Hörhold (Jena) opened the discussion on sterol biosynthesis by describing the distribution of squalene and sterols in microorganisms. The results support the hypothesis that sterols and steroids are very ancient bioregulators, which evolved prior to the appearance of eukaryotes. H. Fischer (Dresden) provided some new data on the biosynthesis of precursors of phytosterols, the identification of which may be useful for taxonomic reasons. The biotechnology of steroid transformation by microbes was reviewed by V. Malik (Richmond). Naturally occurring sterols and their derivatives are of enormous commercial significance, but their supply is rapidly diminishing. Therefore, new ways must be found to utilize the present sources efficiently and to transform other naturally occurring sterols to appropriate products which may be convertible to desired steroids. For this, it will be necessary to 'construct' microbial strains which offer biochemical activities for sterol cleavage linked with capacities suitable for steroid transformation. This aim may be achieved by several approaches, such as selection and enrichment of specific mutants or by recombination with genetic elements carrying information for special sterol or steroid transforming entities.

Much progress has been made in the elucidation of degradative pathways of sterols and bile acids in microorganisms. S. Hayakawa (Okayama) described his recent work on microbial transformations of bile acids. The application of microbial hydroxylation techniques to bile acids has led to successful hydroxylation at 1β, 12β, 15α or 15β. R. Komel (Ljubljana) described the influence of the culture medium on the rate of transformation of cholesterol by *Nocardia* sp. P. Hösel (Jena) added some new results concerning the capacity of *Mycobacterium* sp. to degrade the sterol side chain. L. Träger (Frankfurt/M.) determined the activity of hydroxysteroid-dehydrogenases in extracts of *Streptomyces hydrogenans*. The microbial syntheses of both enzymes were regulated by steroids in a non-coordinate manner. Hantos et al. (Budapest) reported on the induction of steroid-dehydrogenase and steroid-esterase synthesis in *Flavobacterium*. According to their results cultures of the same strain were induced separately under different conditions favouring the synthesis of the two kinds of enzymes, respectively. The bioconversion of the appropriate substrate was performed after combining the two cultures. L. Sedlaczek et al. (Lódź) stressed the usefulness of non-germinating spores of *Cunninghamella elegans* for the transformation of cortexolone to its 11α- and 11β-hydroxy derivatives instead of using traditional methods of steroid biotransformation.

Published by Elsevier Biomedical Press
00145793/82/0000–0000/$02.75

Together with the recombination technique the methodology of using immobilized microbial cells for steroid modification is very useful for gaining sufficient and possibly new steroid compounds for practical use. In his lecture P. Atrat (Jena) gave a survey on typical sterol and steroid transformations using immobilized cells as biocatalysts for steroid-1(2)-dehydrogenation and hydrogenation, hydroxylation and degradative reactions including side-chain splitting. Also he discussed in detail the perspectives of practical applications of matrices and developmental trends in this field. F. Ergan (Compiègne) in co-operation with the research laboratories in Jena investigated two biological approaches for specific modification of steroids. The first approach used immobilized enzymes requiring co-factor regeneration. The second approach included immobilized whole cells. Special efforts were made to get suitable supports for the immobilization. The highest range of progesterone transformation was obtained with calcium alginate as support, but as far as selectivity is concerned, carreghenan or polyurethane gave better results.

M. Oettel (Jena) reminded the participants that the importance of steroid drugs in the production programmes of the pharmaceutical industry will continue in the remote future. There are several demands for better therapy which call for special compounds, e.g., menstruation inducers (anti-gestagens), derepressors of the immune system (anti-glucocorticoids), steroid-coupled cytostatic agents and inhibitors of enzymes, which participate in steroid biosynthesis or metabolism. The pharmacokinetics of contraceptives in women and in experimental animals as well as the role of specific receptor molecules were extensively discussed by G. Hobe (Jena) and I. S. Levina (Moscow). There was general agreement about the necessity to use cultures of human cells in vitro, instead of performing animal experiments in vivo, to get reliable results with regard to both specificity and mode of action and metabolism in human beings. If cell cultures are not available organ explants often will suffice.

Several papers presented in Weimar dealt with very recent investigations on steroids occurring and acting within the brain. They suggest that this rather new field of steroid research may unfold unexpected reactions of steroids including the possible role of neural cell membranes as natural targets of steroids. Both, E. Baulieu (Paris) and H. Breuer (Bonn) added very interesting details to our knowledge of the central action of steroids. The formation and accumulation of dehydroepiandrosterone sulfate in the rat brain depend on in situ mechanisms unrelated to the peripheral endocrine gland system. Catechol-estrogens show non-genomic effects in the brain. G. Dörner (Berlin) reported on the influence of prenatal stress of steroid hormone-dependent permanent changes of sexual behavior of rats. M. Koch (Jena) described a very interesting line of research, which showed that the role of sex steroids in regulation of pituitary hormone release can be interpreted by a theoretical model obtained after computer simulation. The model provides a number of clues for further systematic experiments on the mode of action of endocrine systems.

M. Toth (Budapest) compared the affinity of testosterone, 19-nortestosterone and their 5α-reduced derivatives to the androgen receptors of the rat seminal vesicle and of the skeletal muscle with the androgenic and myotropic activity of the steroids, respectively. The results point to the importance of studying receptor binding at physiological temperature. A. Crastes de Paulet (Montpellier) characterized a specific cytosolic protein in human lymphocytes which binds 25-hydroxycholesterol specifically with high affinity. After translocation to the nucleus 25-hydroxycholesterol inhibits the phytohaemagglutinin-stimulated blastic transformation of lymphocytes.

The final panel discussion confirmed several statements and highlights gained during the symposium. Especially, the evidence that steroids are not only important factors in cell and organ homeostasis, but are also active in cell and organ differentiation which is prone to disarranging influences in all phases of life, was convincingly presented. The central action of steroids corroborates the expectation that steroids do not act only at the genome. The importance of membranes as targets of steroid hormones, however, should be verified biochemically as well as biophysically. Therefore, the co-operation of 'membranologists' is needed in this field. With regard to the genomic action of steroids there is still an urgent need to define the exact role of steroid receptors and their fate within the cell. We are still far from understanding the biochemical meaning of the heterogeneity of receptor proteins within defined target organs.

Of special importance was the attempt to define perspectives in steroid research and application. This includes problems of side effects of contraceptive drugs, or the application of steroids in elderly men and women, e.g., for the treatment of oestoporosis or for substitution of decreasing androgen levels in men.

Moreover, there is a need for better methods for receptor estimation, which are already used as one of the parameters for successful endocrine therapy of various tumours in both sexes. The discrepancy between the results of receptor assays in tumour biopsies and the success of hormonal treatments in vivo confirms once again that the dogma according to which steroid hormones bind to specific receptor proteins in the cytoplasma ên route to the nucleus may well turn out to be an over-simplification.

Both the symposium and the final panel discussion gave an excellent example of the importance of stimulating discussions between scientists with different expertise who start from various points of view, thus facilitating the collection of facts and ideas which are necessary to understand the complexity of steroid biochemistry at present.