HORMONES AND BRAIN DEVELOPMENT

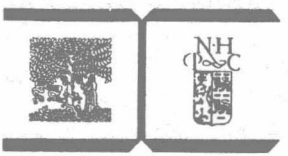
G. Dörner and M. Kawakami
Editors

DEVELOPMENTS IN ENDOCRINOLOGY Vol. 3

HORMONES AND BRAIN DEVELOPMENT

Proceedings of an International Symposium held in Berlin, German Democratic Republic on September 6-8, 1978

G. Dörner *and* **M. Kawakami** *Editors*



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PREFACE

This book contains the Proceedings of a Symposium held in Berlin/GDR on September 6-8, 1978, supplemented by a few contributions of experts who could not attend this meeting. The purpose of this Symposium was to bring together scientists whose work during the last decade has been directed towards the study on effects of hormones on brain development and function.

Hormones may be defined as chemical messengers that are produced in specialized cells and exert biological effects on other cells of the same organism by acting either locally (as local hormones) or on distant target cells (as systemic hormones). In view of this definition, neurotransmitters may be regarded as local hormones of the brain, and two different hormonal actions can be distinguished for neurotransmitters as well as for systemic hormones: (1) temporary, i.e. reversible stimulatory or inhibitory effects on gene expressions and/or enzyme activities in adult life and (2) persistent, i.e. more or less irreversible effects on gene expressibilities, if the hormones act during critical developmental periods, especially of the brain.

Several findings were obtained which suggest that neurotransmitters, which are influenced by the external and internal environment, may even be regarded as direct organizers of the brain. If occurring in unphysiological concentrations and/or turnover rates during brain development they may act as teratogens, giving rise to permanent structural and biochemical changes in distinct regions of the brain associated with permanent dysfunctions of fundamental processes of life, such as reproduction, metabolism, information processing, and even of immune responsiveness. Consequently, many disorders and diseases of the neuroendocrine and immune systems called idiopathic, genuine, primary, essential or cryptogenic thus far may be based on unphysiological conditions in the external, particularly psychosocial environment, and/or the internal, i.e. metabolic and hormonal environment, during critical developmental periods of these systems. Thus teratophysiology, teratopsychology and teratoimmunology should be linked to teratomorphology.

In my opinion, genuine preventive therapy, which is the highest aim in medicine, can be achieved in fact by general improving

the external environment and/or selective correcting the internal environment during critical developmental periods of the neuro-endocrine and immune systems, which are connected with each other. To reach this aim, exact knowledge of the effects of hormones, including neurotransmitters, on differentiation, maturation and function of the brain appears to be a conditio sine qua non.

Publication of this book has been achieved with minimal delay by use of the camera-ready procedure. I gratefully acknowledge the excellent assistance given by Elsevier/North-Holland Biomedical Press.

Günter Dörner

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ROLE OF THE METABOLISM OF STEROID HORMONES IN THE BRAIN IN SEX DIFFERENTIATION AND SEXUAL MATURATION

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I. METABOLISM OF SEX STEROIDS IN THE BRAIN

A lot of recent evidence indicates that testosterone and other androgens undergo extensive metabolic conversions in the central nervous system (CNS). Two major enzymatic systems have been identified: 1) the 5α-reductase pathway; and 2) the aromatizing pathway. The products of these enzymatic reactions may be crucial for androgens to exert their typical effects on the sexual differentiation of the brain.

A. The 5α-reductase pathway.

The biochemical process through which testosterone and androstenedione may be transformed into 5α-androstan-17β-ol-3-one (dihydrotestosterone, DHT), 5α-androstan-3α, 17β-diol (3α-diol) and 5α-androstan-3, 17-dione (androstandione) in the central structures of male animals are summarized in figure 1.

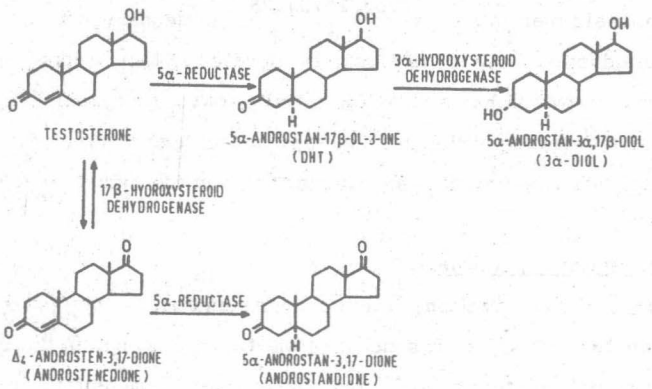

Figure 1. The 5α-reduction of androgens.

These processes have been shown to occur in the anterior pituitary gland as well as in the hypothalamus[1,2,3,4], in the midbrain[5,6], in the limbic system (amygdala and hippocampus)[2,3,4], in the cerebellum[7,8] and in the cerebral cortex[2,3,4,6,8]. Amongst these nervous structures, the hypothalamus appears to possess the highest converting activity. These results have been mainly obtained "in vitro", but have been confirmed also "in vivo"[8,9,10] in several species of animals. These include: the rat[1,2,3,4,5,6,7,9,10], the mice[11], the dog[12], the monkey[8], the beef[13], the guinea pig[14] and the human fetus[15,16]. In the central structures of avian species (chick, European starling, etc.) a 5α-reductase system seems to coexist with a 5β-reductase system[17,18].

In the brain, like in all other mammalian structures (e.g., prostate, seminal vesicles, etc.), the 5α-reduction of testosterone and androstenedione is an irreversible process, and consequently DHT and androstandione cannot be enzymatically converted back to testosterone and androstenedione, respectively[19,20]. On the contrary, 3α-diol may easily revert to DHT, in the anterior pituitary and in the hypothalamus under both "in vitro" and "in vivo" conditions[10 19,20,21].

In male rats, age related changes of the 5α-reductase activity of the central structures have been reported. In the hypothalamus and in the anterior pituitary the 5α-reductase system seems to be more active in neonatal and prepuberal animals than in adults[2,22,23,24,25]. In neonatal and prepuberal rats, the 5α-reductase activity is also very elevated in the cerebral cortex[2, 22,23], a structure which has a very low activity following sexual maturation. The progressive decrease of the 5α-reductase of the central structures from birth to sexual maturity may play an important role in the induction of puberty in this species.

B. The aromatizing pathway.

The process of aromatization, which converts androgens into estrogens, is depicted in figure 2. The presence of aromatizing enzymes in the brain was suggested by Knapstein et al.[26] and subsequently demonstrated by several other investigators. Using either testosterone or androstenedione as the sub-