Paediatric Neuroendocrinology

Edited by: Derek Gupta

with Patrizia Borrelli and Andrea Attanasio

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PAEDIATRIC NEUROENDOCRINOLOGY

PREFACE

By any standard, one of the most dramatic advances in neurophysiology in this decade has been the recognition of the importance of peptides as neurotransmitters and neuromodulators whether in the central nervous system or in the peripheral system. The inescapable upheaval due to this new knowledge has also touched the field of Paediatrics. The first International Symposium on Paediatric Neuroendocrinology, held in Rome in 1983, represents an important contribution to this interchange and stimulation of ideas and developments which are of vital concern to all of us in the fields of paediatrics as well as in neuroendocrinology.

The presence of internationally recognized authorities as speakers and discussion leaders is, we believe, a guarantee that this volume as the Proceedings monograph has brought forth new facts, contrasting view points and perhaps significant conclusions. We also think that this volume is a synthesis of the writing, teaching and lecturing of some of the finest experts in the growing field of paediatrics and developmental neuroendocrinology, in which the speakers so eloquently pleaded for a new understanding of the interdependence of the clinical and experimental disciplines and the need for a new joint endeavour. The experimental knowledge that cell-to-cell communication within the brain is mediated by the secretory products of the neurons has now also become relevant in the clinical assessment.

A great deal of the credit for organizing the Symposium goes to the Study Group for Paediatric Neuroendocrinology and Ospedale Pediatrico Bambino Gesu, Rome. Our appreciation is also extended to Mrs Egidia Naiser who coped with the typewritten scribble to typescript on special paper. Finally we thank our publisher Croom Helm for undertaking the task of publishing this volume.

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TO

NIBU

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Chapter One

SEX DIFFERENCES IN THE BRAIN

H.H. Swanson

INTRODUCTION

The process of mammalian sexual reproduction involves the central nervous system (CNS) in two ways (1) neural control of endocrine function, and (2) appropriate behaviour to allow males and females to get together, mate and raise offspring. Sex differences in the brain like sex differences in body structure, are determined by interaction of genetic, hormonal and environmental factors (for reviews see Booth, 1979; Goy and McEwen, 1980; MacLusky and Naftolin, 1981, McEwen, 1983). The prevalent theory is that in mammals the XY genotype leads to the differentiation of the embryonic gonad into a testis. Androgens secreted by the fetal testes induce differentiation of the internal and external genital system along male lines. Other sexually dimorphic features, such as obvious differences in body size and build, but also more subtle sex differences in blood composition, energy metabolism and liver enzymes may be thus programmed. It is postulated that the developing nervous system is also permanently and irreversibly affected by perinatal testicular hormones.

Under normal conditions, exposure of the developing CNS to androgens results in phenotypic differentiation of neuroendocrine and behavioural responses which are congruent with the genotype, and which are reinforced by postnatal experience (Goy and McEwen, 1980; Jost, 1983). These lead to the development of male patterns of sexual behaviour (masculinization) and suppression of female patterns of gonadotrophin secretion and sexual behaviour (defeminization). The period of maximal susceptibility depends on the stage of maturity of the brain and is independent of the birth process. It seems that the

developing organism has to be exposed to the hormone prior to eye opening for enduring modifications to be produced (Goy and McEwen, 1980). This "organizational" action of sex steroids differs from "activational" effects in the adult which are characteristically excitatory and reversible. It was previously assumed that masculinization and defeminization were part of the same process. Recent findings suggest that these are separate processes involving different CNS regions, different critical periods and different hormone metabolites. Indeed, although masculinization can be induced by androgens in both sexes in all mammals, defeminization only occurs in certain species, primarily rodents, where it produces the well-known syndrome of permanent anovulatory sterility. Since rats and mice have been studied most intensively, this phenomenon might have been attributed more importance than warranted and led to unjustified generalizations. Female primates, including humans do not show disturbances in reproductive function after early exposure to testosterone; they do, however, show masculinization (Karsch et al., 1973).

Whereas masculinization, with or without defeminization follows early exposure to androgen in both sexes, feminization has generally been considered to emerge in the absence of specific hormonal induction. Recent findings do not support the latter assumption and indeed it is possible to produce asexual rats in which both masculinization and feminization have been inhibited after perinatal exposure to estrogen antagonists (Dohler, 1978, 1981). Conversely, since both sexes have the potential for development along either male or female lines, bisexuality may follow simultaneous stimulation of both systems.

THE AROMATIZATION HYPOTHESIS

In the rodent, masculinization of neural functions generally involves intraneuronal conversion of the major testicular hormone, testosterone, to its metabolite estradiol-17beta (Naftolin et al., 1975; McEwen et al., 1977; Jost, 1983). This process, called aromatization, requires specific enzymes which are present in selected neurones in the hypothalamus, preoptic area and amygdala. These brain areas have been shown to be involved in sexually dimorphic neuroendocrine and behavioural functions by lesions, electrical stimulation and local steroid

implantation. These same neurones contain high-affinity estrogen binding macromolecules or receptors which bind the locally produced estradiol. This cytoplasm receptor complex is translocated to the cell nucleus where it alters the expression of the genome (McEwen, 1976; McEwen et al., 1977). Whereas aromatization appears to be essential for sexual differentiation of neuroendocrine function and behaviour in the rat and mouse, this does not necessarily apply to all species. Behavioural masculinization in the ferret, guinea pig and primate is generally mediated by both testosterone and its metabolite, 5a-dihydrotestosterone (DHT) acting directly by binding to intraneuronal androgen receptors. Even in the same species, however, certain sexually dimorphic functions may be differentiated by estrogens and others directly by androgens (Jost, 1983).

ORGANIZATIONAL AND ACTIVATIONAL HORMONE EFFECTS ON BEHAVIOUR

Hormones present during development sensitize the brain to the later activational effects of sex typical hormones, so that females are more likely to show feminine responses to estrogen and progesterone and males masculine responses to testosterone. This applies both to copulatory behaviour *per se* and to many other sexually dimorphic behaviour patterns, some of which differ in degree rather than quality. Activity levels, exploratory behaviour, aggression, maternal behaviour and responses to competition and harassment may vary between sexes. Presumably these sex typical and species characteristic patterns have evolved because in a direct or indirect way they contribute to reproductive fitness. It is probably economic in an evolutionary context that they should be modulated by gonadal hormones in adulthood.

Other behaviour patterns, although programmed by perinatal steroids, do not require further hormonal activation for their expression. A well-known example is the increase in rough-and-tumble play of prepubertal female rhesus monkeys who had been exposed to testosterone prenatally (Goy and Resko, 1972). It has been suggested that these youngsters were treated differently by peers and adults in the social group because of the obvious virilization of their genitalia. However, androgenized females raised in isolation indulged in similar masculine

games.

A third category refers to sexually dimorphic patterns exhibited in response to gonadal hormones in the adult, without having been preprogrammed. Such a situation is analogous to the induction of beard growth in human females by androgens and mammary development in males by estrogen. A behavioural example is the induction of singing in adult female canaries by testosterone. The contrast between behaviour operating entirely through activational mechanisms and that operating through organizational mechanisms suggests that the nature of the hormonal interactions with cellular machinery might contrast correspondingly.

In this context it might be mentioned that until recently estrogen was thought to have only long term indirect effects through changing the genome after nuclear translocation (O'Malley and Birnbaumer, 1978). A direct action of estrogen on the surface of the nerve cell membrane which produces changes in activity within seconds of application has been demonstrated (Moss and Dudley, 1978). Testosterone may be found to work in a similar way.

Other ways in which hormone action may be modulated in the brain is by alterations in neuronal concentration of either aromatizing enzymes (which convert testosterone to behaviourally active estradiol-17B), or in 5B-reductase which inactivates it (Hutchison, 1975). Enzyme activity can be modified by environmental stimuli, suggesting that the hormonal environment of the brain can change quite rapidly in response to diurnal or seasonal changes, as well as to social stress (Lupo di Prisco et al., 1978). Seasonal influences may also affect neuronal cell number, size and receptor content (Konishi and Gurney, 1982).

MORPHOLOGICAL DIFFERENCES IN BRAIN STRUCTURE

The presence of all sorts of sex differences in neural function raised the question as to whether these would be reflected in differences in morphology. Attempts to find gross anatomical substrates for sex differences in behaviour have been largely unsuccessful. Most functions are present in both sexes and sexual dimorphism in behaviour is more a matter of degree than an all-or-none phenomenon. In some song birds, however, the vocal control system is clearly demarcated and sexually dimorphic and so is its function. In the canary and the zebra