STUDIES ON ANDROGEN AND ESTROGEN UPTAKE BY RAT HYPOTHALAMUS

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INTRODUCTION

Sex hormones play a decisive role in the determination of hypothalamic function. In the neonatal rat, the "basic" condition appears to be the female type, in which the hypothalamus, at about the time of puberty, exerts a cycling effect on the sex hormone-dependent cells; this results in the estrous cycle (1,2,3). In male rats this potential cyclic activity of the hypothalamus is irreversibly switched off at, or near to birth by a process that seems to require androgen (4,5). The role of sex steroid-binding proteins in these processes has not been fully delineated and this paper will present data that is pertinent to this topic. An experimental tool that has been much used in the study of hypothalamic development is the neonatally androgenized rat. Injection of certain androgens, notably testosterone propionate, into neonatal female rats produces, in adult life, a state of persistent vaginal estrous, polyfollicular ovaries, cystic glandular hyperplasia of the uterus, sterility and male-type behavior (4,5). Pfeiffer (6), who first discovered this syndrome, thought that it was due to effects on the anterior hypophysis, but it is now known that the main effect is on the anterior hypothalamic-preoptic region of the brain, with the primary effect being on the latter region (5,6). In the adult female rat this region controls the cyclic release of gonadotrophins via the hypothalamus and anterior hypophysis. This is mediated by a positive feedback effect of estrogen associated with external stimuli from other regions of the
brain (8-12); the cyclic release of gonadotropins is superimposed on a tonic mechanism controlled by the basal median eminence (1-3). Neonatal androgenization permanently alters the preoptic region so that it is no longer sensitive to estrogen or electrical stimulation. Permanent changes also occur in other regions of the hypothalamus.

The induction of the constant estrous syndrome can be achieved by administration of a single dose of microgram amounts of testosterone propionate, and, to a lesser extent, certain other androgens, to neonatal female rats; both steroidal and non-steroidal estrogens are also effective (5,14). The data for androgens is summarized in Tables 1 and 2, and as far as the relevance of androgen receptors to the induction of this syndrome is concerned, two points are of interest. Firstly, Ring A-reduced compounds such as DHT* and androstenediol are inactive (14,15), so the "classical" DHT receptor cannot be involved in the androgenization process. Secondly, testosterone propionate is more effective than the free steroid (5,16). The identity of the inducer is not yet known and this point is mentioned further in the discussion.

Two reports suggest that the inductive process requires the presence of inducer for several days (18,19) which is in contrast to the few hours duration suggested by the Gorski group (20,28).

Of particular interest is the observation that the susceptibility of the central nervous system to alteration of its normal pattern of development is restricted to the first ten days of life. Removal of the testes from male rats or administration of testosterone propionate to females is only effective during the first ten days of life (7,22). Even within this period, there is a progressive decline in sensitivity from day one to ten (23).

The relevance of the events precipitated by neonatal androgenization to the physiological mechanism whereby the potential cycling activity of the neonatal male hypothalamus is switched off is still subject to debate. However, there are indications that the amounts of androgen required for the androgenization syndrome are physiologic rather than pharmacologic (5,24).

The present paper will discuss some aspects of estrogen and androgen binding in the androgen-induced constant estrus syndrome.

*Abbreviations used: DHT - 5α-dihydrotestosterone
3H estradiol - 6,7 3H estradiol-17β
3H testosterone (and its propionate derivative) - 1,2 or 1,2,6,7 3H testosterone.