Aromatase in the Central Nervous System

F. Naftolin and Neil J. MacLusky

Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, Connecticut 06510

Abstract

Central (central nervous system and pituitary) aromatization appears to be a fundamental process for endocrine control and development. Metabolism of androgens to estrogens and the subsequent metabolism of estrogens have been proven in many species, including humans, and linked to estrogen action. Thus, aromatization appears to initiate or to be involved in activities of importance to endocrine function at the central level and their effects peripherally.

In the context of breast cancer, central aromatization relates to the control of gonadotrophins and other pituitary-brain hormones which may effect metabolism at the level of the breast. For example, follicle-stimulating hormone can increase aromatization and may be a factor in the control of such metabolism in breast tissues.

Aromatization by Central Tissues

Aromatization of androgens by CNS tissues (Chart 1) has been proven to exist in all species studied thus far (4, 13, 21). The levels of activity are relatively modest compared to tissues classically known as estrogen-producing sources, such as placenta and ovary. However, the evidence for in vitro and in vivo CNS aromatization is firm and includes localization to areas of neuroendocrine activity, particularly the hypothalamus and limbic system. While the anterior pituitary gland has occasionally been shown to form measurable estrogen in vitro, this is less consistent. It is now established that CNS aromatase activity is found in the microsomal compartment, occurs in areas known to contain estrogen receptors, and responds to sex steroids and other endocrine changes. Coupled with evidence of other CNS steroidal and nonsteroidal hormone production, these findings contribute to our acceptance of the hypothalamus and its linked limbic structures as endocrine tissues. The proof of CNS aromatization rests upon 3 types of evidence: direct in vitro studies; direct in vivo studies; and indirect in vivo studies. These data have been reviewed previously and, we will only touch upon details used to tie the biochemical findings to some of the effects of central (CNS and pituitary) aromatization.

Early animal studies led us to the conclusion that one well-known "androgen action," sexual differentiation of the rodent brain (10, 17), required local estrogen formation (22). This "aromatization hypothesis" led to direct in vitro testing of CNS aromatization with time of incubation. Canick et al. (24) showed an increase in in vitro aromatization by turtle CNS with time of incubation. Canick et al. (5) and Vaccaro et al. (26) showed diminution of aromatase activity by cultured hypothalamic neurons under the influence of norepinephrine and isoproterenol. The pregestational antiandrogen cyproterone acetate when given prior to dissection curtails in vitro CNS aromatization (14). No evidence of product inhibition of CNS aromatization by estrogens has been reported. Several groups have shown a change in aromatization during the pre-postnatal period (8, 21); however, the cause of these age-related changes is unknown. The anatomic location of CNS aromatase has been beautifully mapped by microdissection techniques (24).

Implications of Central Aromatization

Central aromatization forms a critical link between biochemical and anatomic aspects of endocrine regulation. The effects of this in situ steroidogenesis are local, but they are amplified by subsequent changes in control of the target organs of the pituitary and of the brain itself. Estrogens (and androgens, probably acting via central aromatization) are important in the study of human brain.
growth of neurites and synaptic circuitry and in the development of neuroendocrine controls. These latter include the timing of sexual maturation, control of sexual behavior, and gonadotrophin regulation (2, 19). Estrogen exposure may also play a role in aging phenomena in the rodent brain (3). Generally, these effects result from the administration of aromatizable androgens or estrogens, and, while a role for androgens per se has not been ruled out, there is clear evidence that aromatase blockers, antisera to estrogens, and nonsteroidal estrogen antagonists can block these activities, while antiandrogens have minimal or no effect (1, 15, 20). Moreover, nonandrogens such as exogenously administered nonsteroidal estrogen agonists and catechol estrogens can produce such effects as sexual differentiation of the rodent brain (17).

Recently, Krey et al. (14, 15) have explored the effects of testosterone on gonadotrophin control and sex behavior in the rat by injecting testosterone and following changes in the hypothalamic content of cell nuclear estradiol, cell ERN, and PRC. When this was done in castrated androgen-insensitive male rats, it was seen that testosterone administration increased hypothalamic nuclear estradiol and both ERN and PRC levels while inducing lordosis behavior and cyclic LH release. After injection of [3H]testosterone, approximately 70% of recoverable nuclear radiolabeled steroid was newly formed estradiol. Krey et al. have also used the aromatase inhibitor androstatrienedione and the nonsteroidal androgen antagonist flutamide in assessing the mechanism of administered testosterone in causing lordosis and cyclic LH release in castrated normal female rats. They found that the actions of testosterone could be blocked by androstatrienedione but not by flutamide and that induced lordosis behavior and cyclic LH release were accompanied by increased ERN and PRC. This work in castrated rats has been mentioned to show some of the in vivo aspects of extragonadal aromatization. Failure of all investigators thus far to prove the existence of measurable aromatization by rat fat plus nuclear localization of estradiol in the hypothalamus of Krey's experimental animals indicates that this model may bear close relevance to events occurring as a result of central aromatization.

Estrogens formed in the brain or elsewhere are important in gonadotrophin homeostasis. Evidence in humans indicates that one can uncouple the feedback effect of testosterone on gonadotrophins by treatment with the estrogen antagonist clomiphene (20). Changes in available estrogen affect gonadotrophin release, and diminished estrogen, whether due to failure of direct gonadal secretion or of available androgen for peripheral conversion, will result in elevated circulating LH and follicle-stimulating hormone. One of the effects of unopposed gonadotrophin secretion might be an increase in peripheral aromatization (6, 9). Breast tissue can aromatize androgens (7, 23), and might respond to this stimulation. The impact of local formation of estrogen by breast tissue has not been assessed; however, estrogens induce local peroxidase formation in uterus (12) and the catechol estrogen-metabolizing enzyme catechol O-methyltransferase is found in high concentration in the breast (11). As well, estrogens and their metabolic products, the catechol estrogens, modulate prolactin secretion (16). While no direct relationship between prolactin and breast neoplasia has been shown, the effects of estrogen and prolactin in stimulating breast growth and functions are undisputed and cannot be overlooked in any such considerations.

**Summary**

Central aromatization has been proven in many species and is present throughout life. It appears to be a fundamental process, the importance of which in determining growth and development of central and peripheral tissues outweighs the relatively small quantitative capacity of this system for steroid metabolism. Central aromatization also furnishes precursor estrogen for subsequent formation of catechol estrogens, some of which are active biological substances. The result of this in situ metabolism of androgens includes intracellular changes in estrogen and progestin receptor status and may be the basis for such endocrine actions as gonadotrophin and prolactin regulation. Thus, the linkage between central aromatization and the biology of the breast may be important for events related to abnormal as well as normal breast function.

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**References**


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