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Androgen effects on the female brain

FSDeducation Group Training Course on "Female Sexual Dysfunction: Hormonal causes and consequences"
6th Amsterdam Menopause and Women's Health Symposium, Amsterdam (The Netherlands), September 26-28, 2010,
Abstract book, p. 71-72

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Androgen effects on the female brain

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Background

For decades, research on the role of sexual hormones on women' and female animal brain has been focused on estrogens, with scant data on androgens (testosterone, androstenedione, dehydroepiandrosterone sulfate/DHEA-S), in spite of the fact that the serum levels of testosterone and of proandrogens exceed that of estradiol, even during peak reproductive years. Only in the last decade the focus has definitely shifted on the role of androgens.

Aim of the presentation

To analyze the current evidence on the role of androgens on women's brain with focus on three main topics:

1. Effect of androgens on neuronal physiology and pathophysiology;
2. Effect on cholinergic (cognition), serotonergic (mood) and dopaminergic (motor) systems;
3. Effect on sexual function, where multiple neurotransmitters are involved.

Method

Literature review plus Authors' clinical experience.

Results

1. Androgens have a powerful **trophic and reparative effect on neurons and glial cells** via a direct (membrane, non genomic) and indirect (genomic) mechanism of action. Testosterone effects are either via the Dehydrotestosterone (DHT) and the AR; via estrogen and the ER, after aromatization; or via conversion of DHT to 3 α -diol and non-genomic signals (GABA-A receptors). Their effect on **neuroplasticity** is the biological correlate of **psychoplasticity**, a key issue when considering the current concern on women's brain aging. As androgens peak at 20s, are halves at 40s with a further decline with increasing age, the issue of the impact of this loss on the brain is of the highest importance, more so in women who underwent bilateral oophorectomy during the fertile age. The evidence on the effects of testosterone and DHEA-S on the female brain is still scant. Specific concern is raised by the long term effect on women's brain and mental functions of aromatase treatment in breast cancer survivors. The evidence is surprisingly lacking.
2. Systems and functions where testosterone have a definite role include:
 - a) the **cholinergic system**, involved in **cognition and memory**: difficulty concentrating is negatively correlated with testosterone. Women who underwent oophorectomy before the onset of menopause had an increased risk of cognitive impairment or dementia compared to referent women (HR = 1.46; 95% CI 1.13 to 1.90; adjusted for education, type of interview, and history of depression). The risk increases with younger age at oophorectomy (test for linear trend; adjusted p < 0.0001);
 - b) the **serotonergic system**, involved in **mood**: estrogen and add-back testosterone have both been shown to positively affect mood and well-being;
 - c) the **dopaminergic system**, involved (also) in **neuromotor competence**, the system most neglected when discussing women's brain: the risk of parkinsonism increases following oophorectomy (OR=1.68; 95% CI 1.06 to 2.67; p = 0.03), with a borderline significance for Parkinson's disease. In particular, there is a linear trend of increasing risk with younger age at oophorectomy.
3. **Androgens have a powerful effect in boosting women's sexual function**. Neurobiology of sexual desire and central (mental) arousal, and the peripheral neurovascular response are substantially modulated by sexual

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hormones. Androgens have a leading role in the initiation and modulation of sexual function, in women as in men. In men they are ten times higher than in women, contributing to the stronger intensity of sex drive in men. Multiple neurotransmitter systems in the brain, especially the areas known to regulate mood and desire (including the amygdala, hippocampus and hypothalamus) are heavily influenced by sex hormones.

Testosterone specifically increases physical and mental energy (which potentiate sexual desire), assertiveness and lucidity; stimulates mental and genital sexual arousal, erotic dreams, voluntary and spontaneous sexual fantasies; increases nipple and genital excitability, of the clitoris and cavernous bodies; reduces the lag-time between the beginning of the fore-play and the achievement of orgasm with a central and peripheral mechanism; increases the intensity and pleasure of orgasm and facilitates the achievement of multiple orgasms.

Conclusion

The women's brain is a key target of testosterone. All brain functions are modulated by androgens. More research is needed to substantiate the role of androgens on neurons and glial cells and the complex benefits appropriate androgen replacement may offer women who want to age mentally at their best.