The female butterflies of the soul: a Journey from sex chromosomes to women's brains

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Structural and functional sexual dimorphisms in neurons, glial cells and subcellular organelle, such as the mitochondria, are involved in the generation of sex differences in behavior and brain pathology. The accepted theory to explain mammalian brain sexual differentiation postulates that testosterone produced by the fetal testes causes brain masculinization. According to this theory, female is the default brain sex in mammals. However, our findings indicate that sexual differentiation of female neurons is an active process that, being driven by sex chromosomes, is independent from ovarian secretions. In female hippocampal and hypothalamic fetal neurons, sex chromosomes determine an accelerated growth of dendrites and axons compared to male neurons. This accelerated neuritogenesis is mediated by an early repression of Notch and upregulation of neurogenin 3 by estradiol locally produced in female neurons by the enzyme aromatase, with independence from ovarian hormones. In contrast, male neurons seem to lack a cellular intrinsic program for sexual differentiation and this process is driven by exogenous testosterone from gonadal origin. In the adult female brain, neuronal production of estradiol participates in the modulation of synaptic and glial plasticity and cognitive function. In addition, aromatase expression and estradiol synthesis are induced *de novo* in reactive astrocytes after traumatic brain injury and stroke. Brain estradiol production under these circumstances is neuroprotective, through mechanisms involving the interaction of estrogen receptors with insulin-like growth factor-1 and Wnt signaling. In contrast, decreased estradiol synthesis in the aged female brain represents a risk factor for the manifestation of cognitive impairment and neurodegenerative diseases after menopause. The identification of new synthetic estrogenic compounds, with enhanced neuroprotective activity and reduced peripheral undesirable effects, offers potential therapeutic avenues to prevent brain deterioration in older women.

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