Development of the Cerebral Cortex: XV. Sexual Differentiation of the Central Nervous System

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Previous columns in this series have described the dynamic interplay between the developing CNS and many neurotrophic and transcriptional factors intrinsic to the CNS. However, for some regions of the CNS this is not the only story. Hormones are also required for the proper development and sculpting of key areas of our brains.

Our current understanding is that the initial blueprint for the development of our brains and bodies is female. During development, however, there are times when one cannot accurately determine the sex of an embryo or fetus on the basis of his/her gonads because they are at an indifferent stage and are identical in the two sexes. Both sexes have the anlage of both male and female internal sex organs. How then do males and females ultimately come to differ anatomically and functionally?

Hormonal influence is part of the answer. Testicular hormones appear to be the principal cause of the masculinization

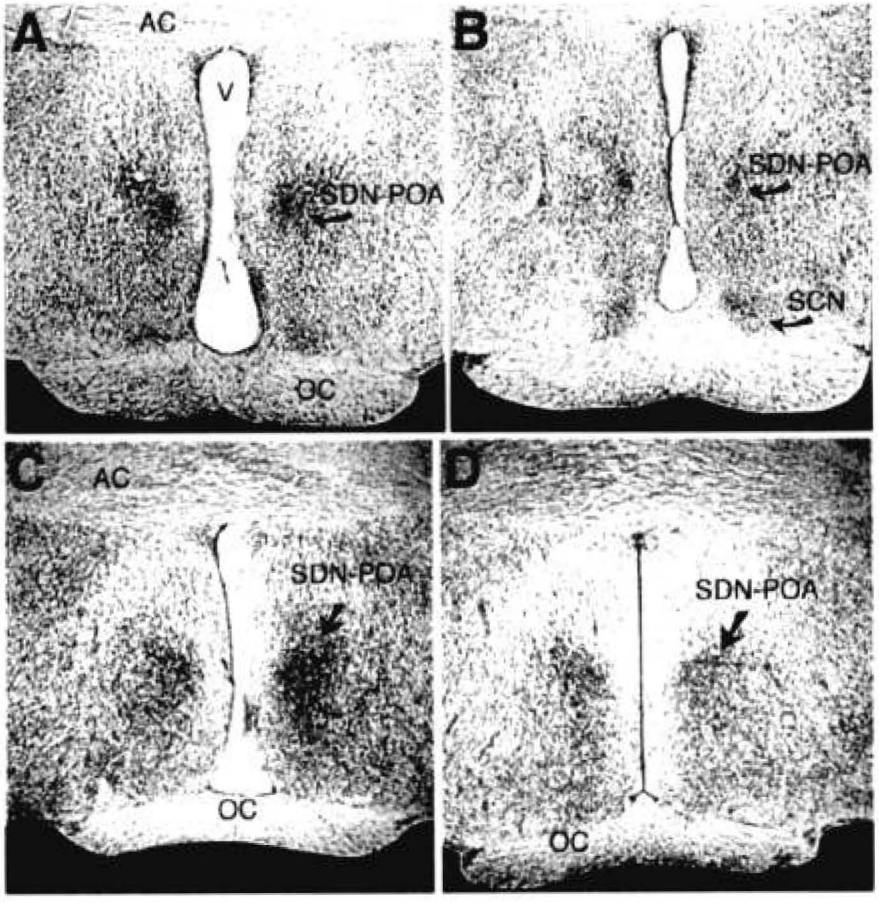

Fig. 1 Representative coronal sections through the sexually dimorphic nucleus of the preoptic area (SDN-POA), a marked and hormone-sensitive structural sex difference in the adult rat. A: male; B: female; C: female treated perinatally with testosterone; D: female treated perinatally with the synthetic estrogen diethylstilbestrol. AC = anterior commissure; OC = optic chiasm; SCN = suprachiasmic nucleus; V = third ventricle. Adapted from *Brain Research*, Volume 302, Dohler KD, Coquelin A, Davis F, Hines M, Shryne JE, Gorski RA, Pre- and postnatal influence of testosterone propionate and diethylstilbestrol on differentiation of the sexually dimorphic nucleus of the preoptic area in male and female rats, pp. 291–295, copyright 1984, with permission from Elsevier Science.

of the feminine blueprint. The differentiation of the anlage of the gonads into the testes is initiated by the *testis-determining gene* located on the Y chromosome. The testes are then able to secrete mullerian duct-inhibiting hormone (MIH), which prevents the development of the oviduct, uterus, cervix, and the deepest part of the vagina. In addition, testosterone is secreted, and it or its reduced metabolite, dihydrotestosterone (DHT), binds to androgen receptors located in the tissues that induce differentiation of the mesonephric duct into the vas deferens and epididymis and masculinize the external genitalia. Males with complete androgen insensitivity syndrome have a total absence of androgen receptors despite having an XY karyotype. These individuals have female external genitalia, inguinal testes, and a female identity. Because MIH action does not require androgen receptors, they have a shortened vagina and no oviduct, uterus, or cervix.

Hormones also lead to sexual differentiation of the CNS. It is clear that in laboratory animals, the CNS is inherently female unless exposed to testicular hormones. Manipulation of the hormonal environment during perinatal development permanently alters both the structure and function of the CNS. Exposing females to testicular hormones masculinizes components of the CNS. Prenatal chemical castration or surgical castration of the male allows the development of a more female-like CNS. In mammals, the sexual differentiation of the CNS has a significant role in shaping sexual preference and other reproductive activities. In addition, it influences food intake and body weight, territorial marking and aggressive behavior, learning strategies, and play behavior. In humans, probably other aspects of cognitive function are affected also.

Given the extensive evidence for the existence of gender-specific differences in CNS function, it is no longer surprising that some structural differences in the CNS of males and females arise from hormonal actions during development. In laboratory animals, sex differences have been documented in the volume and number of neurons in various nuclei in the brain and in at least one spinal cord nucleus. In most of these, but not all, gross nuclear volume and the number of neurons is greater in the male sex. Perhaps the largest and best studied structural sex difference is the sexually dimorphic nucleus of the preoptic area (SDN-POA) of the rat (Fig. 1). Moreover, there are numerous sex differences in synaptic connections between various brain regions and in regional variations of various neurochemicals. Most, if not all, of these sex differences are the result of exposing the developing male CNS to testicular hormones.

Although it would be a logical assumption that testosterone or its metabolite, DHT, is the masculinizing hormone, testosterone secreted by the testes can be aromatized to estrogens. In fact, there is overwhelming evidence that estrogen is actually the masculinizing hormone. The simple notion of sex-specific gonadal hormone production, e.g., testosterone in males and estradiol and progesterone in females, is incorrect. Males and females differ in relative hormonal concentrations and ratios, not sex-exclusive distribution of different hormones.

What about humans? First, prenatal or postnatal manipulations of the hormonal environment to study the resulting developmental changes are clearly unethical. Generally, one must rely on inherent differences between normal male and female individuals. However, individuals do exist who have genetic anomalies that lead to altered development. One example is the androgen insensitivity syndrome in which a genetic male with normal testes cannot respond to testosterone because of the absence of androgen receptors. Such individuals feel that they are female, and this supports a role for gonadal hormones in the sexual differentiation of human brain function. However, to date there have been no studies of the brains of such individuals.

There have been at least 9 reports of structural sex differences in the human brain and 1 in the spinal cord. The following nuclei are larger in age-matched male brains: SDN-POA (also known as the interstitial nucleus of the anterior hypothalamus) and the darkly stained component of the bed nucleus of the stria terminalis (BNST). In females, the central component of the BNST and the midsagittal area of the anterior commissure are larger, the splenium of the corpus callosum is more bulbous, the isthmus of the corpus callosum is larger, and the massa intermedia is more often present than in males, and when present in both sexes the massa intermedia is larger in women. In the spinal cord, Onuf's nucleus is larger in males. In only a few cases have these sex differences in humans been confirmed by independent laboratories, and no information is available on the effects of endogenous or exogenous hormones on these sex differences, either developmentally or in adult life. However, there is growing evidence that fluctuations in adult hormone levels can affect brain structure, and we must hold open the possibility that differences in gonadal hormone levels in the adult could contribute to some differences in brain structure.

We do not have a clear idea of the functional significance of these structural sex differences. Some of these structures, such as the interstitial nucleus of the anterior hypothalamus, are located in an area of the brain known to play a role in the regulation of reproductive behavior. Sex differences in the corpus callosum and perhaps the anterior commissure could be related to interhemispheric communication. In human beings, brain function is more lateralized in males. However, even in laboratory animals, the specific functions of the various sexually dimorphic nuclei are not clear.

Of considerable interest are 3 recent reports of a structural brain difference between homosexual and apparently heterosexual men. One component of the interstitial nucleus of the

anterior hypothalamus is larger in heterosexual men. In addition, the suprachiasmatic nucleus of homosexual men is larger than that of either heterosexual men or women, and the midsagittal area of the anterior commissure is larger in homosexual men than in heterosexual men. Whether these structural differences are causally related to sexual orientation, a consequence of lifestyle or behavior, or merely an unrelated epiphenomenon remains to be determined.

There are also significant gender differences in cognitive function in human beings. As a group, males do better on visual-spatial tasks and in mathematical reasoning while females perform better on verbal tasks, although considerable overlap exists in cognitive abilities of individuals. Nevertheless, the possibility clearly exists that hormonal differences between males and females during critical periods of brain development induce structural differences that permanently affect brain function. Excellence in visual-spatial tasks and mathematical reasoning or verbal tasks may be determined very early in life by hormones through their effects on neuronal growth and synaptic connections.

The mechanisms by which hormones permanently alter brain structure are not clear. It is well documented that gonadal hormones can act as neurotrophic factors that prevent or reduce developmentally regulated cells, a naturally occurring phenomenon that serves to sculpt neural circuits. However, in at least one case, gonadal hormones appear to actually induce apoptosis. In addition, the effects of gonadal hormones on neural development appear to be regionally specific. Although many neurobiologists focus their research on adult males to avoid possible complications due to the cycle of ovarian hormones, some investigators still ignore the sex of their subjects. This is potentially a serious error. In neurobiology in its broadest context, one must assume that there is a functional and/or structural sexual dimorphism until proven otherwise. The brains of men and women and boys and girls do differ to a degree. Overall, the similarities between their brains are most obvious, but sexual dimorphisms in discrete regions of the brain exist and are likely to have significant functional consequences.

WEB SITES OF INTEREST

http://beWEL.com/healthy/sexuality/1998/ga/index.shtml
http://www.life.uiuc.edu/neuroscience/faculty_profiles/Juraska_J Mhtml
http://ajax.abacon.com/books/ab_020514084x.html

ADDITIONAL READINGS

Dohler KD, Coquelin A, Davis F, Hines M, Shryne JE, Gorski R (1984), Pre- and postnatal influence of testosterone propionate and diethylstilbestrol on differentiation of the sexually dimorphic nucleus of the preoptic area in male and female rats. *Brain Res* 302:291–295

Gorski RA (1998), Sexual differentiation of the brain. In: *Reproductive Endocrinology and Biology: Principles of Medical Biology*, Vol 12, Bittar EE, Bittar N, eds. Stamford, CT: JAI Press, pp 1–23

Kimura D (1998), Sex, sexual orientation and sex hormones influence human cognitive function. *Biomed Rev* 7:33–39

LeVay S (1993), *The Sexual Brain*. Cambridge, MA: MIT Press

LeVay S, Hamer DH (1994), Evidence for a biological influence in male homosexuality. *Sci Am* 270:44–49

Matsumoto A, Arai Y (1997), Sexual differentiation of neuronal circuitry in the neuroendocrine hypothalamus. *Biomed Rev* 7:5–15

Swaab DF, Zhou J, Fodo M, Hofman MA (1997), Sexual differentiation of the human brain. *Biomed Rev* 7:17–32

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