

Sexual Differentiation of the Brain

Sexual Dimorphism – structural differences between the sexes

Sexual dimorphisms found in many regions of the brain.

We will focus on sexual differentiation of the hypothalamic-pituitary axis and the role of steroid hormones in sexual differentiation.

In mammals the default is female, with differentiation toward masculine patterns of gonadotropin secretion and behavior occurring in the male as a result of exposure to hormones of testicular origin during development.

In mammals differentiation includes:

1) Defeminization - suppression of female behavioral and cyclic pattern of gonadotropin secretion.

2) Masculinization – enhancement of male characteristics

Landmark study Phoenix, Goy, Gerall, and Young 1959

These authors proposed that testicular steroids could permanently alter the developing nervous system to make it more likely to display masculine behaviors and less likely to display feminine behaviors.

- This irreversible effect was organizational and not activational.
- Exposure of female guinea pigs to androgens in utero reduces their receptivity or female behavior in adulthood.
- What is different about males and females that cause them to behave differently?
Answer: Brains are structurally different.

Aromatization hypothesis

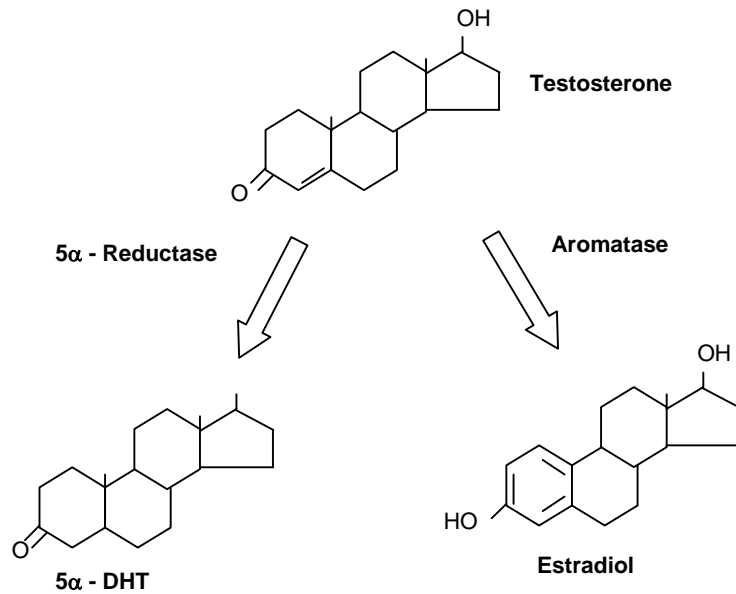
Aromatization hypothesis was originally developed through research with rats.

Observations:

- 1) 5α -DHT is less effective than either testosterone or estradiol to induce defeminization.
- 2) The developing brain is a site of androgen to estrogen conversion
- 3) Inhibition of estrogen formation from androgen or the ability of estrogen to bind to the estrogen receptor impairs sexual differentiation of the brain.
- 4) Estrogen is 1000 times more potent than testosterone.
- 5) A single injection of estradiol benzoate postnatally masculinizes the

volume of the SDN-POA of the female rat.

6) Further evidence that the actions of androgens are not critical in the developing brain came from Tfm male rats. These rats have 85 - 90% fewer androgen receptors than normal littermates, yet gonadotropin release and sex behavior do differentiate with testosterone.



Critical Periods:

From: MacLusky and Naftolin, 1981

Animal	Gestation or Incubation	Critical Period (after conception)
Rat	20 - 22	18 - 27 days
Mouse	19 - 20	Postnatal
Guinea Pig	63 - 70	30 - 37 days
Sheep	145	30 - 90 days
Rhesus monkey	146 - 180	40 - 60 days
Zebra finch	12 - 14	posthatching

Role of estrogen receptors in sexual differentiation

With the identification of a second estrogen receptor (beta) in 1996, it was suggested that the processes of masculinization and defeminization could be regulated by selective activation of either the alpha or beta receptor. It has been shown that these two processes are regulated via two different estrogen receptors.

- Estrogen receptor alpha (ER α) – masculinization
- Estrogen receptor beta (ER β) – defeminization

- ER α KO mice – fewer numbers of males exhibit copulatory behavior.

- ER β KO mice – No difference in male reproductive behavior in WT and KO mice. Both WT and KO mice show copulatory behavior. This indicates that their brains were masculinized.

Morphological Sex Differences

The preoptic area (POA) of the anterior hypothalamus has been implicated in male sexual behavior.

Lesions in the POA of rats caused males to lose interest in mating females.

Dr. Gorski showed that the POA was 5 – 6 times greater in size in male rats compared to females.

- He termed this region sexually dimorphic nuclei –POA (SDN-POA).
- Nucleus of the SDN-POA is visible in rats at 20 days post-fertilization.
- No significant sex differences in the volume of the SDN-POA until day of birth (~ 3 days later).
- During the next 10 days there is a gradual increase in SDN-POA volume in the male.
- Castration of newborn rat produces a significant reduction in the volume of the SDN-POA. Administer testosterone the following day and the reduction in size can be prevented.
- Administration of testosterone to a newborn female rat will increase the volume of the SDN-POA

In humans this region is known as the third interstitial nucleus of the anterior hypothalamus (INAH3). The volume of INAH3 is greater in males than females. The INAH is larger due to greater number of neurons, but these differences are not detected in children younger than 6 years of age.

In sheep the ovine sexually dimorphic nuclei (oSDN) is greater in size in males than females.

The SDN-POA of the rat, INAH3 of the human, or oSDN of the sheep brain have all been speculated to influence male sexual behavior. Specifically, the SDN-POA has been associated with male copulatory behavior and sexual partner preference. It is unknown if these nuclei in the brain are homologous among the species.

Protection Hypothesis

Alpha-Fetoprotein – rats and mice

- A plasma glycoprotein produced by placenta and hepatocytes during fetal life. AFP is in great amounts during fetal life and markedly decreases soon after birth. That alpha-fetoprotein binds specifically to estradiol and not testosterone led to the hypothesis, the fetal female brain is protected from estradiol by alpha-fetoprotein.
- If estradiol were not bound by AFP, estradiol would be free to enter the brain and cause masculinization and defeminization of the female brain.
- Afp^{-/-} female mice show no female sexual behavior. The Afp^{-/-} female mice do not exhibit lordosis behavior. However, administration of an aromatase inhibitor to pregnant females beginning on day 12 of pregnancy restored female sexual behavior in Afp^{-/-} female mice.
- Steroid hormone binding globulin – primates and other mammals

Effects of Sexual Differentiation in Gonadotropin Release

- Males – tonic LH release
- Females – LH surge
- Androgenized Females – treatment with testosterone in utero prevent the LH surge from occurring.

- Female rats exposed to testosterone fail to ovulate.

- Ovaries transplanted to the anterior chamber of the eye in male rats develop mature follicles but do not ovulate. These follicles will ovulate if the male rat is gonadectomized at birth, the critical period of sexual differentiation of the SDN-POA.

- Aromatization of testosterone defeminizes the brain that a LH surge does not occur in either males or androgenized females.

TAKE HOME MESSAGE:

Testosterone from the fetal testis is aromatized to estradiol within the fetal brain. During the critical period estradiol causes organization of the CNS. The organizational effects which occur during fetal development in long gestation species or postnatally in short gestation species are permanent. In contrast the activational effects of the hormones are transient and occur in adulthood, ie puberty. Exposure to testosterone / estradiol during the fetal period masculinizes and defeminizes the brain. Masculinization of the nuclei is essential for male-typical adult behaviors. Defeminization is the loss of adult female-typical behaviors and suppression of estradiol to induce an LH surge.