Hormonal Control of Brain Development and Behavior

- Sexual differences in behavior and brain activity
- Distribution of sex hormone receptors in the brain
- Current hormone levels control seasonal singing and brain morphology in songbirds
- Prenatal exposure to sex hormones affects adult reproductive behavior and brain anatomy
- The organizational hypothesis
- Congenital adrenal hyperplasia
- Progestin-induced pseudohermaphroditism
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Control of Gene Expression by Steroid Hormones

The target cells of steroid hormones have receptor proteins to which the hormones bind. The receptors of many steroids are located in the cytoplasm. The hormone-receptor complex enters the nucleus, where it binds to enhancer steroid response elements associated with many target genes. Together with other transcription factors, the steroid receptors activate or inhibit transcription.
Figure 16.9: Synthetic pathways for vertebrate sex steroid hormones

Testosterone is synthesized via progesterone from cholesterol.

In the presence of the enzyme aromatase, testosterone is converted into estrogen.

In the presence of 5α-reductase, testosterone is converted to 5α-dihydrotestosterone.
Genetic Disorders Interfering with Secondary Sex Differentiation

• Congenital adrenal hyperplasia (CAH) – based on loss-of-function alleles for enzymes converting progesterone to metabolic steroids. Leads to elevated testosterone and masculinization in females.

• Androgen insensitivity – loss of function in X-linked gene for androgen receptor. Allows development of female external genitalia and secondary sex characteristics in males with normal \( SRY^+ \) and (non-descended) testes.

• Guevedoces (penis at 12 years of age) - based on autosomal recessive alleles for 5-\( \alpha \)-reductase, which metabolizes testosterone to DHT. Affects only males.
Figure S16.e: Congenital Adrenal Hyperplasia

This baby girl shows mild enlargement of the clitoris and fused urogenital folds.
Androgen Insensitivity

Individuals with this disorder have normal XY chromosomes except for a mutation in the gene for the androgen receptor. They have (non-descended) testes and produce androgens, but their cells cannot respond.

However, they do respond to estrogen produced in their adrenal glands and elsewhere. As a result, they develop female secondary sex characteristics.
The “guevedoces” of the Dominican Republic are genetically deficient for 5 alpha reductase, leaving males unable to metabolize testosterone to dihydrotesosterone. They do not develop male external genitalia until puberty.

2. Lacking dihydrotestosterone (DHT) in utero, his boy’s external genitalia develop as female. However, internally the gonadal tissue is that of normal male and his karyotype is 46 XY (normal male).

5. With the testosterone surge at puberty, the phenotype changes to male: the voice deepens, the testes descend, the phallus grows, erection and ejaculation begin, and a male psychosexual orientation develops.
Somatic sexual development in mammals

Primary (gonadal) sex differentiation depends on the $Sry^+$ gene, whereas secondary sex differentiation is controlled by sex hormones.
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Figure 17.2: Receptors for sex hormones have distinct distributions in the brain.

Photographs show frontal sections of lizard brains hybridized in situ with probes for mRNAs encoding specific hormone receptors.

Androgen receptor mRNA (top) accumulates in brain areas involved in aggression and copulation, such as AME and NSL.

Progesterone receptor mRNA (bottom) accumulates in areas involved in ovulation and sexual receptivity.

Other brain areas (including MPA) show mRNAs for both receptors.
**Figure 17.3: Sex-specific patterns of brain activity.** The receptors for androgens (AR), estrogen (ER), and progesterone (PR) have *hormone-specific* distributions in the human brain. Differences between the sexes in actual hormone levels lead to *sex-specific* brain activity patterns.
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Figure 17.4: Hormonal control of singing in male zebra finches.
Frequency of singing is shown for normal males (Pre-op), castrated males (Castrate), castrates with implants releasing testosterone propionate (TP), and castrates after removal of TP implants (Post-TP).
Figure 17.5: Sexual dimorphism of song control nuclei in the bird brain. Drawings show paramedian sections, anterior to the left, dorsal surface up. The size of each circle is proportional to the volume of the corresponding brain region in the zebra finch. Dots mark regions that become labeled after injection of radioactive testosterone. The number within each circle indicates the approximate percentage of labeled nuclei within each region.
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Figure S17.a: Sexually dimorphic nucleus of the preoptic area (SDN-POA) of the rat hypothalamus.

The SDN-POA is located on both sides of the third ventricle (V) of the rat brain and is larger in normal males (a) than in normal females (b).

Perinatal treatment of rats with either testosterone (c) or its estrogen metabolite (d) enlarges (masculinizes) the SDN-POA.
Figure 17.6: Location in the human brain of the third interstitial nucleus of the anterior hypothalamus (INAH3)
Figure 17.7: Size of the human INAH3 nucleus

F: presumed heterosexual females
M: presumed heterosexual males

- • infected with HIV
- ▲ not infected with HIV

From LeVay (1991)
Male fetuses affect female neighbors in utero.  
2M vs. 0M female rats

Hormone (estrogen plus progesterone) injections that restore lordosis in ovariectomized females do not cause lordosis in castrated males.
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Organizational Hypothesis

Perinatal exposure to testosterone or its derivatives permanently alters the brain, causing it to function in male-specific ways later in life.
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Progesterone is the precursor of testosterone and its metabolites, 17β-estradiol and 5α-dihydrotestosterone.

Progesterone is also metabolized, via corticosterone (in rodents) or cortisol (in humans) into aldosterone, which regulates the levels of sodium and potassium ions in blood.
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Fig. 17.8: Small sex-specific differences in mean and variance may compound to large differences in the areas of talent or non-talent.
Test scores for mental abilities of individuals with hormonal disorders

Relative to their unaffected sisters, test scores for girls with congenital adrenal hyperplasia or progestin-induced pseudohermaphroditism are shifted towards the male averages.

Males with androgen-insensitivity scored at the level of their normal female relatives in verbal skills but scored lower in spatial skills than normal male or female relatives.

*From Doreen Kimura (1992)*
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