Signaling Cascade & Events Leading to Phenotypic Sex Differences

- Sex determining genes
- Gonadal differentiation

Hormones

Embryo → Neonate → Puberty → Adult

Phenotypic sex differences

Experience
Sexual Differentiation

1. Chromosomal Sex
2. Gonadal Sex
3. Hormonal Sex
4. Brain Differentiation
5. Gender Identity
6. Psychosexual Development
7. Sexual Behavior
Undifferentiated reproductive tract. Both Wolffian and Müllerian ducts are present. Müllerian ducts open in the urogenital sinus at the level of the Müllerian tubercle between the orifices of the Wolffian duct.
Hormonal control of male reproductive tract differentiation

Wolffian ducts are maintained by testosterone (T) produced by Leydig cells. Müllerian ducts regress under the influence of AMH produced by fetal Sertoli cells, acting through the AMH receptor. The urogenital sinus and external genitalia are virilized by dihydrotestosterone (DHT), resulting from the reduction of testosterone by the enzyme 5α-reductase (not shown). T and DHT act through the androgen receptor.
The appropriate regulation of androgen activity is necessary for a range of developmental and physiological processes, particularly male sexual development and maturation.

Excessive production of adrenal androgens can cause premature puberty in young boys and their hypersecretion in females, may produce a masculine pattern of body hair and cessation of menstruation.

Androgen ablation therapy is often combined with treatment with nonsteroidal antiandrogens, such as hydroxyflutamide, to block residual adrenal androgen action.

Androgen Replacement Therapy has been in use for over 60 years to treat patients with male hypogonadal disorders and/or failure of sexual development.

The last decade has witnessed a wider therapeutic role of androgens for nonclassical indications. These include male contraception and depressive states frequently associated with a variety of chronic systemic conditions such as physiological aging.
Core Functions of Testosterone and Dihydrotestosterone in Males
Female and Male Reproductive Tracts

Uterine cavity, Fallopian tube, Ovary, Uterus, Cervical canal, Cervix, Vagina, Vas deferens, Seminal Vesicle, Prostate, Epididymis, Testis.

Fig. 26-12c
The Human Brain: A Major Target for Sexual Differentiation
BOLD signal activation for funny - unfunny cartoons. Clusters of activation were superimposed on a Talairach-normalized brain by using mricro software. Significance of activation was determined by using the joint expected probability distribution (36) with height (P < 0.05) and extent (P < 0.05) corrected for the whole brain. Males demonstrate cortical activation of the temporal-occipital junction (FG/ITG) (BA 37), the temporal pole, and STG (BA 38), as well as the IFG (BA 44). Females show activation of the temporal-occipital junction (FG/ITG) (BA 37), the temporal pole, and STG (BA 38), extending into the DLPFC, IFG, and MFG (BA 44/45/46), as well as subcortical dopaminergic reward regions, including the NAcc.
Female - male activation: time-series analysis of NAcc and DLPFC. Female - male comparison shows greater female activation in the DLPFC, IFG, and MFG (BA 45, 46, and 47), as well as the NAcc. Averaged time-series analysis for funny vs. unfunny activity in a 10-voxel subcluster of the NAcc (stereotaxic coordinates, 6, 2, -4; P < 0.0001) reveals strong female activation during funny stimuli and little activity during unfunny events. Males show low activation during funny stimuli and deactivation during unfunny events.
Disorders of Sexual Differentiation
Intersex Conditions

5-alpha reductase deficiency
Androgen Insensitivity Syndrome (AIS)
Partial Androgen Insensitivity Syndrome (PAIS)
Swyer Syndrome
Aphallia

Congenital Adrenal Hyperplasia (CAH)
Progestin Induced Virilization
Swyer Syndrome

gonadal dysgenesis (partial & complete)
Klinefelter Syndrome
Turner Syndrome
Hermaphroditism
In an isolated village of the southwestern Dominican Republic, 2% of the live births were in the 1970's, guevedoces (actually male pseudohermaphrodites). These children appeared to be girls at birth, but at puberty these 'girls' sprout muscles, testes, and a penis. For the rest of their lives they are men in nearly all respects (see photograph 6 below). Imperato-McGinley et al, 1974
As Nature Made Him

By John Colapinto

Caster Semenya
True hermaphroditism: Both Ovarian and Testicular Cells are present in Gonadal Tissue (Ovotestis)
Female - male activation: time-series analysis of NAcc and DLPFC. Female - male comparison shows greater female activation in the DLPFC, IFG, and MFG (BA 45, 46, and 47), as well as the NAcc. Averaged time-series analysis for funny vs. unfunny activity in a 10-voxel subcluster of the NAcc (stereotaxic coordinates, 6, 2, -4; P < 0.0001) reveals strong female activation during funny stimuli and little activity during unfunny events. Males show low activation during funny stimuli and deactivation during unfunny events. A 477-voxel cluster extending through the DLPFC (peak stereotaxic coordinates, -44, 10, 28; P < 0.05) shows similar male and female response to unfunny stimuli and a noticeably more robust female response when they find the cartoon funny. Sex differences were significant for the NAcc-Funny, NAcc-Unfunny, DLPFC-Funny time-series curves (P ≤ 0.001), but not for the DLPFC-Unfunny curves (P = 0.95).