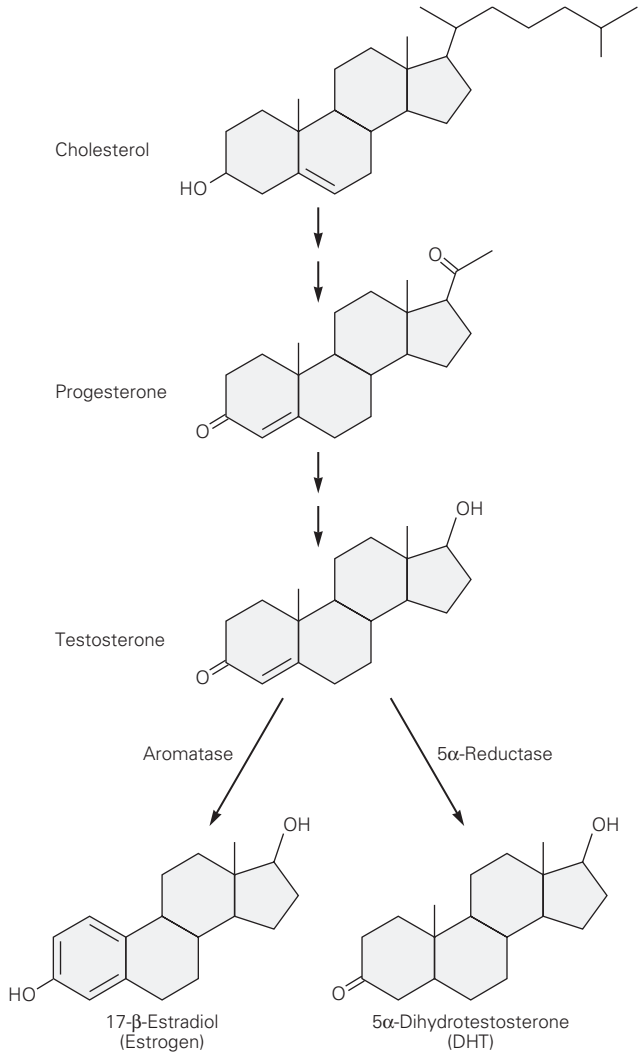

Figure 51–3 Steroid hormone biosynthesis. Cholesterol is the precursor of all steroid hormones and is converted via a series of enzymatic reactions into progesterone and testosterone. Testosterone or related androgens are obligate precursors of all estrogens in the body, a conversion that is catalyzed by aromatase. The expression of 5α-reductase in target tissues converts testosterone into dihydrotestosterone, an androgen.

with a third disorder, complete androgen insensitivity syndrome (CAIS). Testosterone, estrogen, and progesterone are hydrophobic molecules that are able to diffuse across cell membranes, enter the bloodstream, enter cells in many organs, and bind to intracellular ligand-specific receptors. The receptors for these hormones are encoded by distinct but homologous genes.

A single gene encodes a receptor that binds the androgens testosterone and DHT. The androgen receptor binds DHT approximately three-fold more tightly than testosterone, accounting for the greater potency of DHT. There is also a single receptor for progesterone (progesterone receptor), whereas two genes encode receptors that bind estrogens (estrogen receptors α and β). These steroid hormone receptors are present in many tissues of the body, including the brain (Figure 51–4B).

These receptor proteins are transcription factors that bind specific sites in the genome and modulate transcription of target genes. They contain several signature motifs, including a hormone-binding domain, a DNA-binding domain, and a domain that modulates the transcriptional activity of target genes (Figure 51–5A). Hormones activate the transcriptional activity by binding to the receptor. In the absence of ligand, the receptors bind to protein complexes that sequester them in the cytoplasm. Upon binding of ligand, the receptors dissociate from the complex and enter the nucleus, where they dimerize and bind to specific sequence elements in the promoter and enhancer regions of target genes, modulating their transcription (Figure 51–5B).

Patients with CAIS are chromosomally XY but carry a loss-of-function allele of the X-linked androgen receptor that abolishes cellular responses to testosterone and DHT. Because the pathway of sex determination via *SRY* remains functional, these patients have testes. However, because of deficient androgen signaling, the Wolffian ducts do not develop, the testes fail to descend, and the external genitalia are feminized. In adulthood, most of these patients opt for surgical removal of the testes and hormonal supplementation appropriate for females.

Sexual Differentiation of the Nervous System Generates Sexually Dimorphic Behaviors

Sex-specific behaviors occur because the nervous system differs between males and females. These differences arise from a combination of genetic factors, such as signaling pathways initiated by sex determination, as well as environmental factors, such as social experience. In many cases, both genetic and environmental inputs act through the steroid hormone system to sculpt the nervous system. Many instances of sexual dimorphism have been documented, including differences in the numbers and size of neurons in particular structures, differences in gene expression in various neuronal groups, and differences in the pattern and number of connections. Here, we examine a few cases in which studies in experimental animals have provided insights. In later sections, we ask whether similar