Reproduction – testicular function

Rudolf Cardinal, 8 Nov 98.

Testicular compartments (see fig. 3.2 of Essential Reproduction*)*

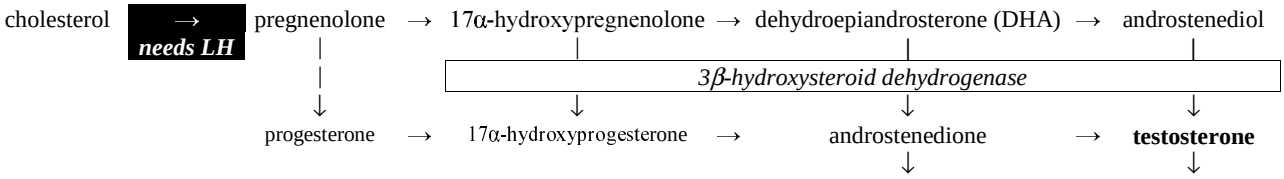
The testis makes (1) spermatozoa; (2) androgens. Spermatozoa are made *within* the seminiferous tubules, while androgens are made *between* the tubules. The testis has four compartments.

- The **intravascular** compartment is in free communication with the **interstitial** compartment. Lymphatics are found here, as are **Leydig cells** that synthesize androgens.
- The interstitial compartment is in restricted communication with the **basal** compartment. This is inside the tubule.
- The tubules are lined by **Sertoli cells.** The main barrier to diffusion is not the boundary of the tubule, but the layer of junctional complexes between Sertoli cells. The basal compartment is between the tubular boundary and the junctional complexes. On the other side of the junctional complexes is the **adluminal** compartment
- This boundary forms the **blood–testis barrier.** This provides a controlled environment for the meiotic stages of spermatogenesis, and prevents leakage of spermatozoal proteins into the blood – the immune system is not tolerized to this genetically different material, and would mount an immune response to it. Further, if an immune response is elicited, the barrier hinders access of immunoglobulins. Breakdown of the barrier leads to *autoimmune orchitis.*

Testicular androgens (fig 3.3)

Leydig cell

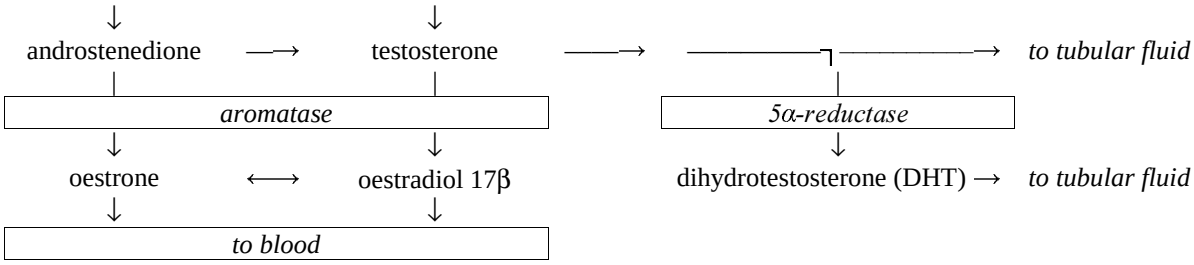
- The top row (the "Δ5 pathway") is predominant in humans.



- Testosterone is released into the blood and lymph, but so are androstenedione (at 10% of the testosterone level) and DHA (6%).
- In addition, as testosterone is fat-soluble, it can pass into the intratubular compartments. Within the Sertoli cells it is bound to an *androgen receptor*. Within the tubular fluid of the adluminal compartment, it binds to an **androgen-binding protein (ABP)** secreted by the Sertoli cells.

Sertoli cell

- Androstenedione and testosterone arrive from the interstitial compartment (Leydig cells). Sertoli cells secrete testosterone and DHT into the seminiferous tubule, but also make oestrogens.



Spermatogenesis – cytodifferentiation

- Spermatogenesis involves *mitotic proliferation* to produce large numbers of cells, *meiotic division* to produce haploid gametes and to increase genetic diversity and *cell modelling* to packages the chromosomes in a "delivery vehicle". 300–600 sperm are produced per gram of testis per second.
- **Mitotic proliferation.** The germ cells of the immature testis (in interphase) are reactivated at puberty to enter rounds of mitosis. They are now known as *stem cells* or *A0 spermatogonia*. They proliferate in the basal compartment. From this reservoir emerge *A1 spermatogonia*, marking the beginning of spermatogenesis. Each A1 spermatogonium undergoes mitosis to produce a 'clone' of daughter cells.[1] The different stages look different and are given names (unimportant) but the resulting cells are called *resting primary spermatocytes.*
- **Meiosis.** The resting primary spermatocytes (diploid, 2n) duplicate their DNA (4n) and then push their way through the tight junctions between Sertoli cells into the adluminal compartment. The first meiotic division results in two daughter *secondary spermatocytes* (2n). The second meiotic division is when the chromatids separate, and results in a total of four *early spermatids* (haploid, n). Cell loss will occurs during these stages.
- **Packaging (spermiogenesis).** The spermatid DNA is condensed (becomes heterochromatic) and packaged tightly. The cytoplasm is remodelled to form a *tail* (propulsion), *midpiece* (contains mitochondria), *acrosome* (for egg penetration) and a *residual body* which acts as a dustbin for unwanted cytoplasm and is phagocytosed by the Sertoli cell after the *spermatozoon* departs.

- Spermatogenesis occurs in close association with Sertoli cells. The spermatocytes and spermatids adhere to the Sertoli cell and indent its cytoplasm. The Sertoli cell is probably involved actively in sperm modelling.
- As meiosis and spermatogenesis proceed, the spermatogenic cells are moved towards the lumen. When spermatid elongation is complete, the Sertoli cell retracts and releases the immature spermatozoa into the tubular fluid.
- The fluid within the seminiferous tubule is actively secreted by Sertoli cells. (If the outflow of fluid from the tubules to the epididymis is blocked, the hydrostatic pressure builds up, dilates the tubules and leads eventually to pressure necrosis of the tubular cells.)

Spermatogenesis – organization

- Spermatogenesis, from entry into first mitosis to the release of spermatozoa, takes 64 days in man. The rate is very constant in a given species, and seems independent of any hormonal control.
- A stem cell will not create clones continuously, but pauses between each clone. It embarks on a new clone at a very precise rate – 16 days in man. This is called the **spermatogenic cycle.** As a result, there are four (64/16) stages of spermatogenesis occurring in the progeny of a given stem cell at any one time.
- However, if this occurred in synchrony throughout the testis, then the animal would only be fertile every 16 days! Instead, different parts of the seminiferous tubule are out of sync with each other. Patches of epithelium tend to be in sync with each other, so the spermatogenic cycle is amplified into the **cycle of the seminiferous epithelium** (a *temporal* cycle; a whole patch cycles as one). Adjacent patches are out of sync.
- In the rat, the synchronised patches form rings around the tubule, so the tubule is divided into segments. Furthermore, adjacent patches enter spermatogenesis sequentially, giving rise to a **spermatogenic wave** (*spatial*) along the tubule. This doesn't happen in humans, where the patches are randomly distributed. This has no functional effect!

Endocrine control of spermatogenesis

- Although androgens and spermatozoa are synthesized in different compartments, spermatogenesis requires androgens. Without testosterone, spermatogenesis ceases.
- **Luteinizing hormone (LH)** causes Leydig cells to make testosterone (it's a glycoprotein and acts via ↑cAMP).
- **Prolactin** binds to receptors on Leydig cells and may enhance the LH effect, but it will not stimulate testosterone production on its own.
- Testosterone enters the tubules and binds, both as testosterone and after conversion to DHT, to androgen receptors in the Sertoli cells. This is required for spermatogenesis. (Note that Sertoli cells make DHT. DHT is a more powerful androgen than testosterone and does not escape from the tubules in appreciable quantities.)
- In addition, **follicle stimulating hormone (FSH)** is required for fertility.[2] FSH stimulates Sertoli cells to synthesize proteins and testicular fluid. Specifically, FSH stimulates the synthesis of androgen-binding protein (ABP).
- While FSH and testosterone have roles in spermatogenesis, they are *permissive* – they determine whether, not how, spermatogenesis takes place.

[1] In the rat, there are six divisions so the maximum clone size is 64 – but not all cells survive so the clone is smaller in practice. In addition, one of the clone cells may revert to being a type A1 spermatogonium and thus serve as a second source of stem cells (in addition to the A0 cells). This may be the most important source of stem cells in the adult!

[2] Humans. There's a species difference – FSH is not *as* crucial in rats, but is required to restart spermatogenesis once it's stopped and is required for maximal fertility in any case.

Regulation of testicular function

Compare to ovarian control. Testicular control is much simpler.

- There is *no positive feedback*. Steroid production is continuous.
- A pulsatile GnRH signal from the hypothalamus causes synthesis and secretion of FSH and LH from the pituitary.
- **Testosterone inhibits LH/FSH secretion.** This involves effects at both the hypothalamus and pituitary. (That's basically it!)
- There may possibly be secretion of inhibin from Sertoli cells that inhibits FSH release selectively. Unproven.

OVERVIEW – Periods requiring androgens; their effects.

Prepubertal

- Androgens are required for prenatal sexual differentiation at foetal age 7w-9m [precise timing uncertain as control of descent of testes into scrotum is unknown].
- Testosterone high in males from birth to 3-5m. Function unknown.
- Adrenal androgens increase from age 8-13y ('adrenarche'); function unknown other than to promote pubic/axillary hair growth.

Accessory sex glands	Wolffian duct differentiation and growth
External genitalia	Growth and differentiation (scrotum and penis)

Pubertal

- Required for sexual maturation at puberty [age 12-18y]
- Required for maintenance of sexual function (inc. spermatogenesis) and appetite in adult [18y-death].

Skeletal muscle	Masculine body growth and physique via enhanced protein synthesis; sodium/potassium/water retention
Bone	Bone formation; epiphyseal closure; calcium, sulphate, phosphate retention
Vocal cords	Voice change
Skin	Hair growth (beard, axilla, chest, pubic, general body surface) Hair loss (e.g. forehead) Sebaceous gland growth, sebum production
Testis	Sertoli cell maturation and androgen-binding protein synthesis Spermatogenesis (requires FSH+testosterone to initiate and testosterone to maintain)
External genitalia	Penile and scrotal growth
Accessory sex glands	Prostate gland, seminal vesicle, bulbourethral gland growth and secretion
CNS	Sexual activity (↑ libido) [note also indirect effects on behaviour via conversion to oestrogen in brain]
Hypothalamo-pituitary axis	Inhibition of LH secretion