DRAFT DETAILED REVIEW PAPER

ON

STEROIDOGENESIS SCREENING ASSAYS AND ENDOCRINE DISRUPTORS

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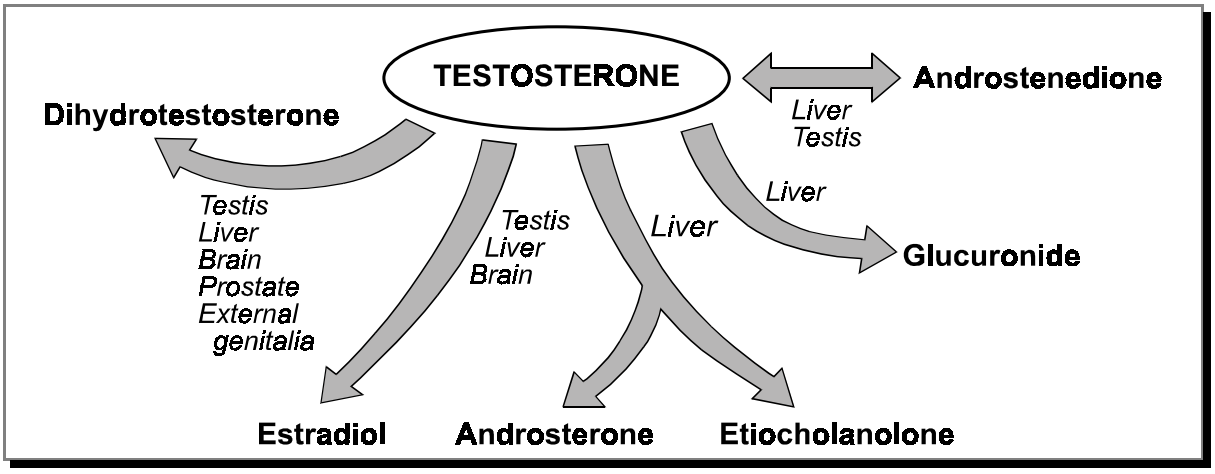


Figure 3-3. Testosterone Conversion in Peripheral Tissues

Source: Federman (1981)

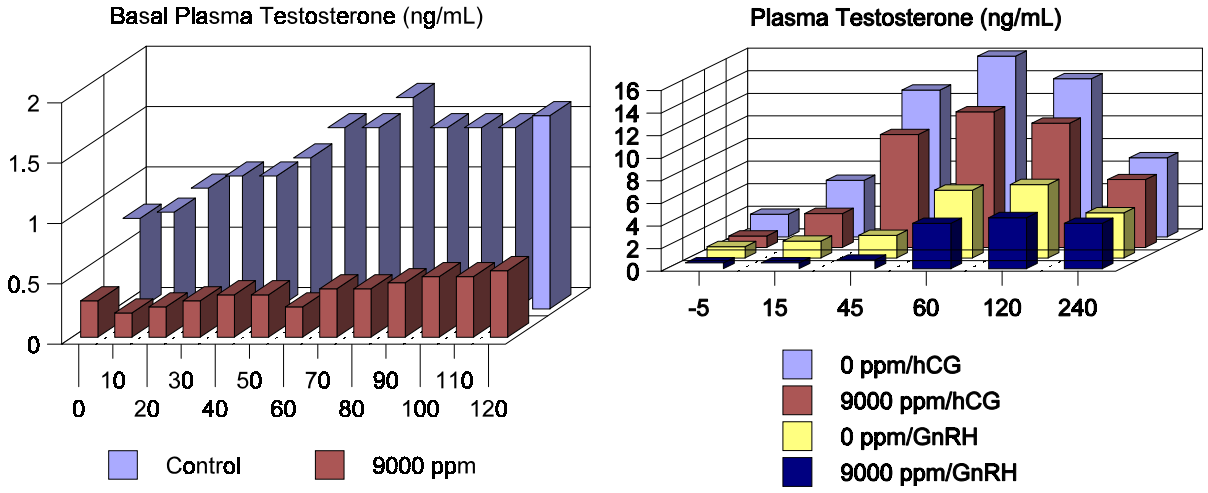
In the female, biosynthesis of the reproductive system steroid hormones occurs in the ovary (Carr and Wilson, 1994). Several cell types in the ovary participate in the synthesis of these steroid hormones. Two of the cell types are follicular cells, the granulosa and theca interna. A third cell type that has been implicated in steroid hormone synthesis is the interstitial cell. These cells are located between the follicles. A fourth cell type is the luteal cells of the corpus luteum, which is formed from the post-ovulatory follicle. Different cell types within the ovary can have varying amounts of given enzymes resulting in some types of cells producing more of one steroid hormone than another. For example, the corpus luteum, which contains primarily theca interna cells and fewer granulosa cells, is the primary source for progesterone and 17β-hydroxy progesterone.

3.2.2 Steroidogenic Biosynthetic Pathway

For the purposes of this DRP, the steroidogenic pathway will have a defined starting point and will include a specified set of chemical reactions that result in the production of gonadal intermediary and end-product hormones. More specifically, the steroidogenic pathway will be those processes in the testis or ovary that occur after stimulation of the gonadotropic receptor. The pathway (1) begins with intracellular signal transduction, (2) continues with cholesterol production in the cytoplasm and transport to the mitochodrial inner membrane, and (3) ends with a set of multi-step enzymatic conversions from cholesterol to the end-product hormones. Each of these stages is described below in further detail and each will also appear in later discussions about the sites of action of substances that disrupt steroidogenesis.

3.2.2.1 Signal Transduction. Signal transduction describes the intracellular biochemical reactions that occur after stimulation of the LH membrane bound receptor and up to initiation of cholesterol transport to the mitochondria. The intracellular pathways that constitute the signal transduction phase are illustrated in Figure 3-4.

A study using ECT for determining whether boric acid had androgenic or anti-androgenic activity was conducted by Fail and coworkers (Fail et al., 1992; 1998; Anderson et al., 1992). Data from this study are shown in Figure 4-2.



PANEL A **PANEL B**

Figure 4-2. Example Data from an ECT Assay

Notes: Sprague-Dawley rats, cannulated to collect serial blood samples (every 10 minutes for 2 hours) for serum hormone analysis, were treated with boric acid in the feed at a concentration of 0 or 9000 ppm for 2, 9, or 14 days. Gonadal response to trophic stimulation was tested by administering GnRH, 25 ng, iv or hCG, 2.5 IU, iv. Basal serum testosterone was decreased 3- to 5-fold at all collection time points (Panel A). Even after challenge with GnRH or hCG, serum testosterone remained lower at most time points (Panel B). Serum FSH was increased about 2-fold for the boric acid group on Day 14 but not at Days 2 or 9. Serum FSH concentrations increased at all time points in response to GnRH stimulation (data not shown). The investigators concluded that boric acid compromised steroidogenesis and the ability of the testis to respond to gonadotropin stimulation.

Source: Fail et al., 1998

Other studies in the literature that use the ECT for evaluating the androgenicity of a substance are summarized in Table 4-2.