Hormonal Control of Male Sexual Function

A majority of the control of sexual functions in the male (and the female) begins with secretions of gonadotropin-releasing hormone (GnRH) by the hypothalamus. You may remember that the hypothalamus is driven by the limbic system, and therefore many psychological factors can influence the release of GnRH. GnRH stimulates the release of two other hormones, luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the anterior pituitary.

Both LH and FSH are glycoproteins that exert their effect on the testes, which in turn activate specific enzyme systems in the testes. LH stimulates the interstitial cells of Leydig to synthesize and secrete testosterone. The majority of the circulating testosterone is made by the Leydig cells. FSH binds to the receptors on the Sertoli cells in the seminiferous tubules where it causes the Sertoli cells to grow and secrete spermatogenic substances. Testosterone and dihydroxytestosterone (DHT) enter into the interstitial spaces of the seminiferous tubules where they have a strong effect on spermatogenesis. Therefore, FSH and testosterone are the regulators of spermatogenesis. The Sertoli cells also secrete a glycoprotein hormone called inhibin in respond to spermatogenesis occurring to rapidly. This hormone decreases the secretion of FSH and GnRH. (inhibins are also secreted by the ovary.)
There is a symbiotic relationship between the brain and testosterone. Many of the central nervous system functions are regulated by testosterone, among them is behavior and cognition. The inputs to the central nervous system, such as psychological stress, can lower the release of GnRH, and therefore decrease serum testosterone levels. Low serum testosterone is also a component of insulin resistance. A research study in 2009 concluded that low serum testosterone was independently associated with insulin resistance in non-diabetic older men.²

From a functional medicine perspective, it’s important to assess for environmental factors that can influence testosterone level. Since over 90% of the testosterone is produced in the testis by the Leydig cells, it important to assess for factors that might inhibit Leydig cell production of testosterone. Disruption of androgen biosynthesis and actions by environmental endocrine disrupting compounds can inhibit critical cellular processes controlling steroidogenesis in the Leydig cells. Disruption can occur with the transport and delivery of cholesterol to the mitochondria, interference with the enzymatic activity along the steroidogenesis pathway, or by interfering with the androgen receptor.

### Natural and Synthetic Chemicals Affecting Leydig Cell Function

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Proposed target</th>
<th>Application or source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procymidone</td>
<td>Androgen receptor antagonist</td>
<td>Fungicide, control of plant diseases</td>
</tr>
<tr>
<td>Linuron</td>
<td>Androgen receptor antagonist</td>
<td>Herbicide, postemergence control of weeds in crops</td>
</tr>
<tr>
<td>Vinclozolin</td>
<td>Androgen receptor antagonist</td>
<td>Fungicide</td>
</tr>
<tr>
<td>p,p’ DDT</td>
<td>Androgen receptor antagonist</td>
<td>Pesticide</td>
</tr>
<tr>
<td>Dioxins</td>
<td>Aryl hydrocarbon receptor agonist</td>
<td>By-product of chlorinated hydrocarbons</td>
</tr>
<tr>
<td>Phthalates</td>
<td>Peroxisome proliferator-activated receptors (PPARs)?</td>
<td>Plasticizers</td>
</tr>
<tr>
<td>Genistein</td>
<td>ERs stimulator</td>
<td>Soy-derived food</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>ERs stimulator</td>
<td>Red wine, red grape</td>
</tr>
<tr>
<td>Bisphenol A</td>
<td>ERs stimulator</td>
<td>Synthesis of polycarbonate plastics</td>
</tr>
</tbody>
</table>

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On the table above you will notice that compounds that stimulate estrogen receptors affect Leydig cell function. The inhibitory effect of estrogens on male reproductive function appears to be mediated by suppression of LH. A direct effect of estrogen on Leydig cell steroidogenesis has also been demonstrated.³
The action of endocrine disrupting compounds on Leydig cell function and the reproductive potential is a complex process that depends on the exposure route, dose, the developmental stage of the target organism and many other factors. Together, these factors determine the potential risk for adverse consequences with long-lasting effects on the male reproductive function.

Together with Leydig cells, adult rat germ cells are able to express P450arom mRNA, which is translated as a biologically active enzyme involved in estrogen production. Consequently, germ cells not only produce estrogens but contain estrogen receptors as well, which would explain part of the role (autocrine and/or paracrine) of estrogens in male germ cell development. The mechanism of action of estrogens in the reproductive organs of the male remains to be clarified, as well as the regulation of aromatase gene expression, especially in germ cells during testicular development. Nevertheless, we have begun to understand the physiological roles (as well as the pathological effects) of these female hormones in males, and, obviously, their involvement in several steps of sperm production and maturation. Thus it is anticipated that parts of male gonadal function are not only androgen regulated but also estrogen controlled in mammals.
Male Infertility

Research studies between the late 1930’s and the mid-1990’s have found a substantial decline in sperm concentration and sperm quality among men living in industrialized countries. Observational studies and animal research suggest that exposure to various environmental pollutants may be contributing to this decline in male fertility, possibly by exerting estrogenic or other endocrine-disrupting effects.  

Suspected Contributing Factors to Male Infertility

- Toxins from cigarette smoke
- Alcohol and drugs that lower sperm count (cocaine, marijuana, [certain antifungals, antihypertensives, and antibiotics] cimetidine, methotrexate, sulfasalazine and others)
- Heavy metal – lead mercury and cadmium
- Obesity – excess body fat converting testosterone to estrogen
- Environmental toxins – bisphenol a, phthalates, vincolozolin (fungicide), pesticides, dry-cleaning agents, and others.
- High soy intake
- Oxidative stress – spermatozoa are highly sensitive to oxidative stress because of their high concentration of polyunsaturated fatty acids and inability to repair damages membranes.
- Hypothyroidism
- Celiac disease and food allergy
- Poor diet

Advanced Lab Testing Considerations for Male Infertility

Aside from primary lab testing, advanced functional medicine test should be considered as indicated by the patient history, physical examination and primary lab testing. The functional/advanced tests of consideration include:

- Organic acid test
- Toxicity Profile test
- RBC Nutrient and Toxic Elements
- Urinary Porphyrin test
- Celiac test/Food allergy
- ASI test
- RBC fatty acid test
**Treatment and Nutritional Considerations**

The main treatment include: optimizing liver function, far-infrared sauna treatment, optimal fatty acid balance and the use of antioxidants.

- Zinc
- L-Arginine
- L-carnitine and acetyl-L-carnitine
- Vitamin E
- Selenium
- Vitamin C
- Lycopene
- B vitamins
- Essential fatty acids

**References**

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9. *Nutritional Influences in Estrogen Metabolism*, 2001, Douglas C. Hall, MD
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