17-Beta-Hydroxysteroid Dehydrogenase
By Ronald Steriti, ND, PhD
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Metabolism
17-beta-hydroxysteroid dehydrogenase (17β-HSD) converts
- Estrone into Estradiol
- Testosterone to Androstenedione
Androstenedione is an intermediate of androsterone, etiocholanolone, and estrone.

Deficiency
Boys with a deficiency of 17β-HSD fail to form testosterone, androstenediol, and estradiol in a normal manner. At puberty, the plasma concentrations of testosterone and DHT will be low, and plasma androstenedione and estrone will be elevated.

Types
There are 14 types of 17β-HSD enzymes. (Gonzalez, Cos et al. 2008) (Vihko, Herrala et al. 2006) (Lukacik, Kavanagh et al. 2006)
17HSD1 catalyzes the reduction of estrone to estradiol with NADP(H) as a cofactor and is mostly expressed in breast tumor tissue. (Miettinen, Mustonen et al. 1996)
17HSD2 catalyzes the oxidation of estradiol to estrone with NAD(H) as a cofactor and is expressed in normal epithelium of the breast but is frequently lost in malignant cells.
High expression of 17HSD1 and amplification of HSD17B1, the gene coding for 17HSD1, as well as low expression of 17HSD2 have been associated with decreased survival in estrogen receptor (ER)-positive breast cancer. (Jansson, Delander et al. 2009)
High expression of 17β-HSD types 1, 2 and 4 is seen to correlate with bad prognosis in breast, colon and prostate tumors, respectively. (Meier, Moller et al. 2009)
One study found pronounced increases in 17HSD10 levels to 179% in multiple sclerosis and to 573% in Alzheimer disease when compared to the age-matched controls. (Kristofikova, Bockova et al. 2009)

Breast Cancer
Reductive 17beta-hydroxysteroid dehydrogenases (17beta-HSDs) catalyze the last step in estrogen activation and are thus critical in breast cancer development. 17beta-HSD Type 1 (17beta-HSD1) is of great importance since it efficiently synthesizes the most potent estrogen estradiol, as well as other estrogens as 5-androstene-3beta,17beta-diol and 5alpha-androstane-
3beta,17beta-diol, and inactivates the most active androgen dihydrotestosterone (DHT), all contributing to the stimulation and development of breast cancers. (Aka, Mazumdar et al. 2009)

**Natural Therapies**

**Cinnamic acids**

Research studies show that flavonoids, their biosynthetic precursors (cinnamic acids and coumaric acid), and their derivatives inhibited 17ß-HSD type 1 and type 5. (Brozic, Kocbek et al. 2009) (Brozic, Lanisnik Risner et al. 2008) (Brozic, Golob et al. 2006)

**Phytoestrogens**

Among naturally present substances, phytoestrogens are the most potent inhibitors of 17ß-HSDs. (Meier, Moller et al. 2009) (Morrissey and Watson 2003) (Adlercreutz 2002) (Deluca, Krazeisen et al. 2005)

**Vitamins C and E**

Cadmium administration caused an increase in reactive oxygen species (ROS) by elevating testicular malondialdehyde (MDA) and decreasing the activities of testicular antioxidant enzymes such as glutathione peroxidase and superoxide dismutase. The mRNA of Steroid Acute Regulatory (StAR) protein was substantially reduced. The activities of testicular delta5-3beta and 17-beta-hydroxysteroid dehydrogenases (HSD) as well as serum testosterone level were also lowered, suggesting that cadmium-induced ROS inhibit testicular steroidogenesis. Supplementation with vitamin C (VC) and or vitamin E (VE) reduced testicular ROS and restored normal testicular function in Cd-exposed rats. (Sen Gupta, Sen Gupta et al. 2004)

**Vitamin E**

A significant diminution in the activities of testicular delta 5, 3 beta-hydroxysteroid dehydrogenase (HSD) and 17 beta-hydroxysteroid dehydrogenase (HSD) along with significant reduction in the plasma level of testosterone and number of spermatogonia-A (ASg), preleptotene spermatocytes (pLSc), midpachytene spermatocytes (mPSc) and step 7 spermatids (7Sd) at stage VII of spermatogenic cycle were observed following cyclophosphamide treatment. Oxidative stress was also noted in testis, which was enlightened by significant elevation in the level of malondialdehyde (MDA) and conjugated dienes along with significant reduction in the activities of testicular peroxidase and catalase. Co-administration of alpha-tocopherol succinate in cyclophosphamide-treated rats resulted a significant restoration of all the above-mentioned parameters to the control level. The results of our experiment suggest that cyclophosphamide treatment at its clinical dose is associated with antigonadal activities as well as induction of oxidative stress in gonad that can be ameliorated significantly by alpha-tocopherol succinate co-administration. (Ghosh, Das et al. 2002)

**Vitamin C**

In the presence of indomethacin (inhibitor of cyclooxygenase) and nordihydroguaiaretic acid (NDGA) (inhibitor of lipoxygenase), the activity of 3 beta-hydroxysteroid dehydrogenase (3 beta-HSD) and 17 beta-hydroxysteroid dehydrogenase (17 beta-HSD) were both inhibited. The
LH-stimulated increase in secretion of testosterone and progesterone was also inhibited by indomethacin and NDGA. On the other hand, vitamin E (antioxidant and inhibitor of lipoxygenase), stimulated the activity of both 3 beta-HSD and 17 beta-HSD and enhanced LH-stimulated androgen production. The metabolites of lipoxygenase (15-HPETE, 15-HETE, 5-HPETE and 5-HETE) and cyclooxygenase (PGF2 alpha) pathways stimulated 3 beta-HSD and 17 beta-HSD activity and enhanced the secretion of progesterone and testosterone. (Reddy, Prasad et al. 1993)

**Vitamin B6**

Pyridoxine hydrochloride significantly increased the activity of 5 alpha-R, 3 alpha- and 17 beta-HSD, but pyridoxal hydrochloride had an inhibitory influence on 5 alpha-R and showed no effect on 3 alpha-HSD activity at the prostate level. (Kniewald, Zechner et al. 1992)

**Licorice**

Oral administration of shakuyaku-kanzo-toh, glycyrrhizin, and glycyrrhetinic acid decreased in vitro basal testosterone production in Leydig cells by LH stimulation. Glycyrrhizin and glycyrrhetinic acid caused a significant decrease in testosterone production with an accumulation of 17 alpha-hydroxyprogesterone when incubated with isolated Leydig cells, while paeoniflorin showed no such effect. The inhibitory effect of glycyrrhetinic acid was far more potent than that of glycyrrhizin, causing about 90% inhibition at 10 micrograms/ml. Glycyrrhizin and glycyrrhetinic acid did not change the cyclic AMP or progesterone level in the Leydig cells. When 14C-labeled androstenedione was incubated with microsomal fraction of testicular or ovarian tissue, glycyrrhizin and glycyrrhetinic acid inhibited the conversion of androstenedione to testosterone, indicating that these compounds inhibit the activity of 17 beta-hydroxysteroid dehydrogenase (EC. 1.1.1.64). The ED50 of glycyrrhetinic acid was about 4 microM. (Sakamoto and Wakabayashi 1988)

**Genistein**

Mammalian lignans and genistein decrease the activities of aromatase and 17beta-hydroxysteroid dehydrogenase in MCF-7 cells. (Brooks and Thompson 2005)

**Retinoic Acid**

A recent study showed that retinoic acid (RA) regulates 17beta-hydroxysteroid dehydrogenase type 2 expression in endometrium by the interaction of RA receptors with specificity protein (SP) 1/SP3 for estradiol metabolism. (Cheng, Yin et al. 2008)

**Cyclophosphamide and Vitamin E**

An older study examined the protective role of alpha-tocopherol-succinate (pro-vitamin-E) in cyclophosphamide (Cytoxan, an anti-cancer drug) induced testicular gametogenic and steroidogenic disorders. A significant diminution in the activities of testicular delta 5, 3 beta-hydroxysteroid dehydrogenase (HSD) and 17 beta-hydroxysteroid dehydrogenase (HSD) along with significant reduction in the plasma level of testosterone and number of spermatogonia-A (ASg), preleptotene spermatocytes (pLSc), midpachyten spermatocytes (mPSc) and step 7 spermatids (7Sd) at stage VII of spermatogenic cycle were observed following cyclophosphamide treatment. Oxidative stress was also noted in testis, which was enlightened by
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References


