3Beta-Hydroxysteroid Dehydrogenase

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3-β-hydroxysteroid dehydrogenase/Δ-5-4 isomerase (3-β-HSD, 3-beta HSD) is an enzyme in the adrenal gland. It is the only enzyme in the adrenal pathway of corticosteroid synthesis that is not a member of the Cytochrome P450 family.

Metabolism

The 3-beta HSD complex is responsible for the conversion of:
- pregnenolone to progesterone
- 17-alpha-pregnenolone to 17-alpha-progesterone
- dehydroepiandrosterone (DHEA) to androstenedione
- androstenediol to testosterone
- 5alpha-DHT to 5alpha-Androstan-3b,17b-diol (3beta-Adiol)

NAD and NADH

3-β-HSD catalyzes the chemical reaction:

\[ 3\beta\text{-hydroxy-} \Delta 5\text{-steroid} + \text{NAD}^+ \rightleftharpoons 3\text{-oxo-} \Delta 5\text{-steroid} + \text{NADH} + \text{H}^+ \]

Thus, the two substrates of this enzyme are 3β-hydroxy-Δ5-steroid and \text{NAD}^+, whereas its 3 products are 3-oxo-Δ5-steroid, \text{NADH}, and \text{H}^+.

Ovulation

3 beta-HSD activity increases during the follicular phase of the menstrual cycle, which results in increased androstenedione, the principal C19 steroid produced by the ovulatory follicle that serves as a substrate for estradiol production. This increase in 3 beta-HSD activity may be important for the associated changes in the late follicular phase that lead to ovulation. (Readhead, Lobo et al. 1983)

Congenital Adrenal Hyperplasia

A deficiency of 3-β-HSD type II form through mutations in HSD3B2 is responsible for a rare form of congenital adrenal hyperplasia.

Newborns affected by 3 beta-HSD deficiency exhibit signs and symptoms of adrenal insufficiency of varying degrees associated with pseudo-
hermaphroditism in males, whereas females exhibit normal sexual differentiation or mild virilization. (Simard, Rheaume et al. 1995)

Elevated ratios of 5-ene- to 4-ene-steroids appear as the best biological parameter for the diagnosis of 3 beta-HSD deficiency. (Simard, Rheaume et al. 1995)

Non-Classical Deficiency

Late-onset (non-classic) 3-beta-hydroxysteroid dehydrogenase deficiency (NCAH) is considered rare.

Post-ACTH increased serum delta 5-17-hydroxyprogrenolone and increased ratio of delta 5-17-hydroxyprogrenolone/17-hydroxyprogesterone are the most sensitive indicators of non-classical 3 beta-HSD deficiency. (Nishi 1990)

Non-classic or mild 3 beta-hydroxysteroid dehydrogenase (NC3 beta-HSD) deficiency may be due to secondary adrenal biosynthetic defects, rather than dual inherited deficiencies. (Tajima, Nishi et al. 1997)

Polycystic Ovary Syndrome

A study found that the hormonal phenotype of non-classic 3 beta-hydroxysteroid dehydrogenase (HSD3B) deficiency in hyperandrogenic females is associated with insulin-resistant polycystic ovary syndrome and is not a variant of inherited HSD3B2 deficiency. (Carbunaru, Prasad et al. 2004)

A report described 15 new menarcheal women affected with non-classical 3 beta-HSD deficiency. Polycystic ovarian syndrome was noted in approximately half the cases. Glucocorticoid treatment greater than 3 months duration results in a reversal of symptoms in most cases. (Schram, Zerah et al. 1992)

Hirsutism

An older study found partial adrenal 3 beta-hydroxysteroid dehydrogenase deficiency is the cause of hirsutism in peri- and post-pubertal hirsute women with hyper-androgenism. (Pang, Lerner et al. 1985)

Male-Pattern Baldness

One study found substantial 3beta-HSD activity present in the cytosol, and cytosol of bald glands showed increased 3beta-HSD activity, the increased conversion of dehydroepiandrosterone to androstenedione may be a critical step for androgenic action and may be responsible for excessive androgenicity in male-pattern baldness. (Sawaya, Honig et al. 1988)
Male Gynecomastia

A case report described an adult male with normal gonadal function presenting with post-pubertal gynecomastia due to 3B-HSD deficiency. (Cavanah and Dons 1993)

Conventional Treatments

Glucocorticoids

Exogenous glucocorticoid therapy suppresses adrenocorticotropic hormone (ACTH) secretion, decreasing pregnenolone, 17-hydroxypregnenolone, and dehydroepiandrosterone (DHEA) levels.

Longer-acting preparations, such as prednisone and dexamethasone, are difficult to titrate and can lead to overtreatment and growth suppression.

Mineralocorticoids

Exogenous mineralocorticoid therapy is required in patients with salt-losing variants of CAH (21-hydroxylase deficiency and 3-beta–hydroxysteroid dehydrogenase deficiency). Plasma renin levels are elevated in patients with untreated salt-losing variants, and the addition of mineralocorticoid replacement normalizes both renin and ACTH levels.

Combination therapy of mineralocorticoid plus glucocorticoid replacement reduces total glucocorticoid dose required and improves statural growth.

Testosterone (boys) or Estradiol (girls)

Children with 3β-HSD CAH may be unable to produce adequate amounts of testosterone (boys) or estradiol (girls) to effect normal pubertal changes. Replacement testosterone or estrogen and progesterone can be initiated at adolescence and continued throughout adult life.

Trilostane

Trilostane (Vetoryl) is an inhibitor of 3 β-HSD used in the treatment of Cushing's syndrome. It was withdrawn from the United States market in April 1994. However, it was approved in 2008 for the treatment of Cushing's disease in dogs. (Komanicky, Spark et al. 1978)

Triiodothyronine, T3

Triiodothyronine stimulates 3beta-hydroxysteroid dehydrogenase activity in the porcine corpus luteum. (Gregorasczuk, Kolodziejczyk et al. 1999)
Natural Therapies - Attenuation

Lithium

Lithium acts on adrenomedullary activity probably by stimulating the release mechanism of epinephrine and norepinephrine from the adrenal gland of rats, but stimulates adrenocortical activity by stimulating both synthesis (including 3 beta-HSDH activity) and release of corticosterone. (Chaudhuri-Sengupta, Sarkar et al. 2003)

Vitamin A

All-trans-retinoic acid (ATRA) strongly induced the expression of steroidogenic acute regulatory protein (StAR) and 3beta-hydroxysteroid dehydrogenase (3beta-HSD) (an increase of 5- and 50-fold, respectively) in human glial GI-1 cells. (Kushida and Tamura 2009)

Gold Chloride

Gold chloride (0.5 mg/kg injected s.c.) treatment for 26 days caused a significant increase in plasma testosterone (p < 0.001) along with stimulation of testicular Delta5-3beta-HSD activity (p < 0.001) and 17beta-HSD activity (p < 0.001) in immature rats. (Biswas, Chattopadhyay et al. 2004)

Significant increase in ovarian and uterine weight and stimulation of ovarian delta5-3beta-hydroxysteroid dehydrogenase (delta5-3beta-HSD) activity and elevation of serum estradiol level were observed following gold chloride (0.2 mg/kg body weight/day), s.c. administration in immature female albino rats. (Chattopadhyay, Sarkar et al. 2006)

Ginkgo biloba

Compared with the type 2 diabetes group, 12 weeks of Ginkgo biloba extract treatment caused very slight pathological changes in the Leydig cells of type 2 diabetic rats, significantly increased the concentrations of blood LH and T, markedly elevated the levels of mRNA in StAR and P450scc and induced an ascending tendency of the expressions of P450c17, 17beta-HSD3 and 3beta-HSD1. (Wu, Wang et al. 2008)

Natural Therapies - Inhibition

Testosterone

Testosterone can act directly on the adrenal gland to decrease 3betaHSD activity. (Stalvey 2002)
Forskolin

Co-treatment with forskolin and angiotensin II resulted in a dose-dependent reduction in cortisol and DHEA secretion concomitant with a marked attenuation of 3 beta-HSD and P450c17 expression. (Bird, Imaishi et al. 1996)

Vitamin E

Testicular tissue from male rats given a vitamin E deficient diet for 91 days showed considerably less 3-beta-hydroxysteroid dehydrogenase activity than did tissue from control rats, but the difference was not statistically significant. (Barnes and Smith 1975)

Alcohol

Ethanol may inhibit testicular steroidogenesis by suppressing at least two steps in the pregnenolone-to-testosterone pathway, the pregnenolone-to-progesterone step catalysed by NAD+-dependent 5-ene-3 beta-hydroxysteroid dehydrogenase/isomerase and the 17-hydroxy-progesterone-to-androstenedione step catalysed by the NAD+-independent C17-20 lyase. (Akane, Fukushima et al. 1988)

Chronic ethanol ingestion increases testicular 17 alpha-hydroxylase and 17,20-lyase and reduces 3 beta-hydroxysteroid dehydrogenase/isomerase in rat testicular microsomes. (Chiao, Johnston et al. 1981)

Cadmium

Cadmium (Cd) is one of the environmental pollutants that affect various tissues and organs including testis. Harmful effect of cadmium on testis is known to be germ cell degeneration and impairment of testicular steroidogenesis.

Zinc and Garlic

In a recent study, the effect of diallyl sulfide (DAS), a sulfur-containing volatile compound present in garlic, and zinc (Zn) was investigated on cadmium-induced testicular toxicity in rats. Male adult Wistar rats treated with cadmium (2.5 mg/kg body wt, five times a week for 4 weeks) showed decreased body weight, paired testicular weight, relative testicular weight, serum testosterone, luteinizing hormone, follicle-stimulating hormone, and testicular total antioxidant capacity (TAC) and protein levels. Testicular steroidogenic enzymes, such as 3beta-hydroxysteroid dehydrogenase (3beta-HSD) and 17beta-hydroxysteroid dehydrogenase (17beta-HSD), and marker enzymes, such as sorbitol dehydrogenase (SDH), lactate dehydrogenase (LDH), acid phosphatase (ACP), alkaline phosphatase (ALP), and glucose-6-phosphate dehydrogenase (G6PD), showed a significant decrease in activities whereas that of gamma-glutamyl transferase was
significantly increased after cadmium exposure. The results have revealed that concurrent treatment with DAS or zinc restored key steroidogenic enzymes, SDH, LDH, and G6PD and increased testicular weight significantly. DAS restored the TAC level and increased testosterone level and relative testicular weight significantly. Zinc restored testicular protein level and body weight. (Sadik 2008)

**Lipoic acid and Selenium**

Serum testosterone, luteinizing hormone and follicle-stimulating hormone levels significantly decreased in the Cd(2+)-exposed rats. The activities of testicular key androgenic enzymes, 3beta-hydroxysteroid dehydrogenase and 17 beta-HSD significantly decreased in Cd(2) exposed rats compared to the control counterparts. In addition, the activities of testicular marker enzymes were significantly altered in cadmium-treated animals. Significant reductions in body and testicular weight as well as antioxidant status were also observed in Cd(2+)-exposed rats. Moreover, some testicular metal levels were altered. Lipoic acid and selenium significantly increased serum testosterone level and restored testicular activity of 3beta-HSD and 17 beta-HSD and were effective in modulation of most of the measured biochemical parameters. (El-Maraghy and Nassar 2010)

**Vitamin C**

Ascorbic acid supplementation restored testicular 3beta-hydroxysteroiddehydrogenase (HSD) and 17beta-HSD enzyme activities, 3beta-HSD and cytochrome P450 side chain cleavage (P450(scc)) mRNA levels and serum testosterone concentration to normal in Cd-administered rats. (Sen Gupta, Kim et al. 2004)

**Vitamin C and Vitamin E**

The activities of testicular delta5-3beta and 17-beta-hydroxysteroid dehydrogenases (HSD) as well as serum testosterone level were 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)

**Lead**

Lead directly inhibited steroidogenesis by decreasing Steroidogenic Acute Regulatory protein expression and the activities of P450scc and 3beta-HSD enzymes with a dose-response trend in MA-10 cells. (Liu, Lai et al. 2001)
**Glutathione**

Depletion of glutathione (GSH), an abundant Leydig cell intracellular antioxidant, might result in reduced testosterone production. Buthionine sulfoximine treatment reduced Leydig cell GSH content by 70% and the ability of the Leydig cells to produce testosterone by more than 50%. As with aging, decreases were seen in LH-stimulated cAMP production, steroidogenic acute regulatory protein, cholesterol side-chain cleavage, 3beta-hydroxysteroid dehydrogenase, and 17alpha-hydroxylase/17,20-lyase. (Chen, Pechenino et al. 2008)

**Carbendazim**

Carbendazim (methyl-2-benzimidazole carbamate, MBC) a metabolite of benomyl is one of the most widespread environmental contaminant of major concern to human and animal reproductive health. The present investigation was undertaken to study the impact of carbendazim exposure on Leydig cell functions. Testis weight, serum testosterone and estradiol were significantly decreased. In addition to this, Leydig cellular activities of steroidogenic enzymes such as 3beta-HSD, 17beta-HSD, antioxidant enzymes SOD, CAT, GPx, GR, GST, gamma-GT, G-6-PDH and non-enzymatic antioxidants such as GSH, vitamins E, C and A were significantly diminished, whereas LPO and ROS were markedly elevated. (Rajeswary, Kumaran et al. 2007)

**Polychlorinated biphenyls**

Polychlorinated biphenyls (PCBs) are ubiquitous and persistent environmental contaminants that disturb normal endocrine functions, including gonadal functions in humans and mammals. PCBs can act directly on Leydig cells to diminish testosterone production by inhibiting gene expression of steroidogenic enzymes and antioxidant system.

Cytochrome P(450)scc, 3beta-HSD, and 17beta-HSD mRNAs were drastically decreased in both 10(-8) and 10(-7) M Aroclor 1254 treatment. (Murugesan, Balaganesh et al. 2007)

Polychlorinated biphenyl (PCB) inhibited 3ss-hydroxysteroid dehydrogenase (3ssHSD), stimulated 17alpha-hydroxylase/lyase (P450c17). (Andric, Kostic et al. 2000)

**Vitamins C and E**

Aroclor 1254 (a PCB) treatment significantly reduced the serum LH, FSH, testosterone, estradiol and androgen binding protein. In addition to this, Leydig cell androgen and estrogen receptors were markedly decreased. RT-PCR analysis of StAR mRNA level did not alter Aroclor 1254 treatment while steroidogenic enzymes such as cytochrome P(450)scc, 3beta-HSD and 17beta-HSD mRNAs were drastically decreased in Aroclor 1254 treatment.
However, the simultaneous administration of vitamins C or E in Aroclor 1254-exposed rats resulted a significant restoration of all the above-mentioned parameters to the control level. (Murugesan, Muthusamy et al. 2007) (Murugesan, Muthusamy et al. 2005)

**Arsenic and Vitamin C**

Arsenic-treated mice showed decreased epididymidal sperm counts and testicular weights compared to untreated mice. These effects were reversed in mice that were co-treated with ascorbic acid. Similarly, arsenic treatment lowered the activities of testicular 3beta-hydroxysteroid dehydrogenase (HSD) and 17beta-HSD, which play important roles in steroidogenesis, and this was reversed by co-treatment with ascorbic acid. The testicles of arsenic-treated mice had decreased glutathione (GSH) levels (which correlate inversely with the degree of cellular oxidative stress) and elevated levels of protein carbonyl (a marker of oxidative damage to tissue proteins). Ascorbic acid co-treatment reversed both of these effects. (Chang, Jin et al. 2007)

**Fluoride, Calcium and Vitamin E**

Fluoride contamination of drinking water can disrupt male gametogenesis and steroidogenesis and induce testicular oxidative stress. Treatment of rats with sodium fluoride at the dose of 20 mg/kg/day for 28 days resulted in significant diminution of testicular Delta5,3beta-hydroxysteroid dehydrogenase (HSD) and 17beta-hydroxysteroid dehydrogenase (HSD) activities and low plasma levels of testosterone, follicular stimulating hormone (FSH) and leutinizing hormone (LH). Co-administration of calcium and Vitamin-E with fluoride resulted in a significant recovery from testicular disorders and oxidative stress in the testis and male accessory sex organs. (Sarkar, Maiti et al. 2006)

**Licorice**

One study found that dexamethasone, glycyrrhetinic acid (from licorice) and spironolactone inhibited 3 alpha/beta,20 beta-hydroxysteroid dehydrogenase. (Itoda, Takase et al. 2002)

**Zinc**

Induced zinc deficiency in male albino rats caused a great reduction in the testicular levels of testosterone as compared to control and zinc-supplemented rats. A great reduction in the activity of 3 beta-hydroxysteroid dehydrogenase, an important enzyme involved in testosterone biosynthesis, was demonstrated histochemically in the testes of zinc-deficient rats as compared to both control and zinc-supplemented ones. (Mansour, Hafiez et al. 1989)
Biochanin A

Biochanin A, found in red clover and soy, was the only phytoestrogen that displayed any dose-dependent inhibition of 3beta-HSD. (Lacey, Bohday et al. 2005)

Isoflavonoids

Isoflavonoids inhibit 3beta-HSD. (Le Bail, Champavieer et al. 2000)

Genistein

Genistein inhibited 3beta-HSD activity (0.2 micromol L(-1) pregnenolonone) with half-maximal inhibition or a half-maximal inhibitory concentration (IC(50)) of 87 +/- 15 (human) and 636 +/- 155 nmol L(-1) (rat). Genistein's mode of action on 3beta-HSD activity was competitive for the substrate pregnenolongrge and noncompetitive for the cofactor NAD(+). On the other hand, equol only inhibited human 3beta-HSD by 42%, and had no effect on 3beta-HSD and 17beta-HSD3 in rat tissues. (Hu, Zhao et al. 2010)

Genistein and daidzein have direct effects on porcine granulosa cell progesterone synthesis which involve the inhibition of 3beta-HSD enzyme activity across the post-cyclic AMP pathway. (Tiemann, Schneider et al. 2007)

The isoflavone derivatives daidzein, genistein, formononetin and biochanin A inhibited 3beta-HSD type II activity at a concentration of 10 microM and of these, genistein was the most potent inhibitor. (Ohno, Matsumoto et al. 2004) (Ohno, Nakajima et al. 2003)

The flavonoids 6-hydroxyflavone, daidzein, genistein, biochanin A and formononetin strongly and significantly inhibited microsomal 3beta-HSD II activity at concentrations from 1 to 25 microM, and I(50) values were estimated to be 1.3, 2, 1, 0.5 and 2.7 microM, respectively. (Ohno, Shinoda et al. 2002)

A survey of more than 30 isoflavones and structurally related compounds revealed that daidzein, genistein, biochanin A and formononetin inhibit both the dehydrogenase and isomerase activity of 3beta-hydroxysteroid dehydrogenase. Inhibition is potent and concentration dependent. IC(50) values determined for these compounds range from 0.4 to 11 microM, within the plasma and urine concentration ranges of daidzein and genistein of individuals on vegetarian diet or semi-vegetarian diet. (Wong and Keung 1999)

Gossypol

Gossypol C30H30O8 is a polyphenol derived from the cotton plant (genus Gossypium, family Malvaceae). Gossypol is a polyphenolic aldehyde that
permeates cells and acts as an inhibitor for several dehydrogenase enzymes. It is a yellow pigment.

Gossypol enantiomers were more potent inhibitors of rat 3beta-HSD with IC(50)s of approximately 0.2microM compared to 3-5microM in human testes. However, human 17beta-HSD3 was more sensitive to inhibition by gossypol enantiomers, with IC(50)s of 0.36+/0.09 and 1.13+/0.12 for (-)- and (+)-gossypols, respectively, compared to 3.43+/0.46 and 10.93+/2.27 in rat testes. (Hu, Zhou et al. 2009) (Pankajakshy and Madambath 2009)

A 1929 investigation in Jiangxi showed correlation between low fertility in males and use of crude cottonseed oil for cooking. In the 1970s, the Chinese government began researching the use of gossypol as a contraceptive. Their studies involved over 10,000 subjects, and continued for over a decade. They concluded gossypol provided reliable contraception, could be taken orally as a tablet, and did not upset men's balance of hormones.

In the mid-1990s, the Brazilian pharmaceutical company Hebron announced plans to market a low-dose gossypol pill called Nofertil, but the pill never came to market. Its release was indefinitely postponed due to unacceptably high rates of permanent infertility. Between five and twenty-five percent of the men remained azoospermic up to a year after stopping treatment. The longer the men had taken the drug and the higher their overall dosage, the more likely the men were to have lowered fertility or to become completely infertile. In 1998, the World Health Organization's Research Group on Methods for the Regulation of Male Fertility recommended that research should be abandoned. In addition to the other side effects, the WHO researchers were concerned about gossypol's toxicity: the toxic dose in primates is less than 10 times the contraceptive dose. (Coutinho 2002) (Coutinho, Athayde et al. 2000) (Waites, Wang et al. 1998)

**Summary**

The 3-beta HSD complex is responsible for the conversion of:

- pregnenolone to progesterone
- 17-alpha-pregnenolone to 17-alpha-progesterone
- dehydroepiandrosterone (DHEA) to androstenedione
- androstenediol to testosterone
- 5alpha-DHT to 5alpha-Androstane-3b,17b-diol (3beta-Adiol)

The reaction requires NAD+, which is converted into NADH+H

Decreased: Testosterone, Alcohol, Arsenic, Cadmium, Fluoride, Lead, PCBs, Forskolin, Licorice, Vitamin E deficiency, Glutathione deficiency,
Zinc deficiency, Biochanin A (red clover and soy), Genistein, Gossypol (cotton), Trilostane (Vetoryl)

Increased: All-trans-retinoic acid (ATRA), T3, Lithium, Zinc and Garlic, Lipoic acid and Selenium, Vitamins C and E, Gold chloride, Ginkgo biloba
References


