

11-Beta-Hydroxysteroid Dehydrogenase

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The intracellular enzyme 11-beta-hydroxysteroid dehydrogenase (11 β -HSD) catalyzes the inter-conversion between biologically active cortisol and inactive cortisone. There are two distinct isozymes: 11-beta-HSD type I and II.

Figure 1: [Progesterone.jpg](#)

Causes of Increased 11-beta-hydroxysteroid dehydrogenase Activity:

- Obesity
- Insulin resistance

Causes of Decreased 11-beta-hydroxysteroid dehydrogenase Activity:

- Apparent mineralocorticoid excess symptoms
- Licorice (glycyrrhetic acid) supplementation
- Carbenoxolone ingestion
- Dithiocarbamates inhibit type II 11 beta dehydrogenase, but not type I

11-Beta-HSD Type I

Type I acts mainly as a reductase producing active cortisol from cortisone in cells. It amplifies the effect of glucocorticoids, whereby free cortisol is generated from the relative excess of circulating free cortisone. This enzyme also plays an important role in the xenobiotic carbonyl compound detoxification processes. 11-beta-HSD type I is expressed in a wide array of tissues, with highest levels in the liver and adipose.

11-Beta-HSD Type II

11-beta-HSD type 2 functions as a dehydrogenase inactivating cortisol into cortisone. It irreversibly catalyzes the dehydrogenation of active 11-beta-hydroxycorticoids before they occupy mineralocorticoid receptors (MR) and thus, allows for aldosterone selectivity for inherently nonselective MR. 11-beta-HSD type 2 is expressed in a wide array of tissues. Highest levels are found in mineralocorticoid target cells such as the renal and outer medullary collecting ducts

Disease Associations

Cushing's Syndrome

Both animal and human studies have demonstrated that alterations in 11-betaHSD type I activity in liver and adipose tissues are associated with metabolic syndrome, possibly reflecting a tissue-specific (omental) Cushing's syndrome. (Anagnostis, Athyros et al. 2009) (Schnackenberg 2008)

Obesity

Increased adipocyte 11-beta-HSD type I is a common mechanism for visceral obesity. (Wiegand, Richardt et al. 2007)

One study found that alterations in 11HSD1 and hepatic 5alpha-reductase activity are associated with generalized, rather than central, obesity in humans. Indices of obesity (body mass index, whole-body percentage fat, waist/hip ratio) were associated with higher urinary excretion of 5alpha- and 5beta-reduced cortisol metabolites (for percentage fat, $P < 0.05$ and $P < 0.01$, respectively) and increased adipose 11HSD1 activity ($P < 0.05$). (Westerbacka, Yki-Jarvinen et al. 2003)

Diabetes

Pharmacological inhibition of 11-beta-HSD type I activity provides an interesting mechanism for the possible development of therapeutic agents to treat type-2 diabetes mellitus. (Hughes, Webster et al. 2008)

Hypertension

Mice deficient in 11HSD type 2 have hypertension and impaired endothelial nitric oxide activity. 11HSD2 may influence vascular function by directly by limiting glucocorticoid-mediated inhibition of endothelium-derived nitric oxide. (Christy, Hadoke et al. 2003) (Yang and Zhang 2004)

A recent study found that a mere three-fold increase in the concentration of the natural glucocorticoid cortisol (from 30 to 100 nmol/L) significantly decreased the expression level of eNOS in human endothelial cells. (Liu, Mladinov et al. 2009)

Atherosclerosis

Selective inhibitors of 11beta-hydroxysteroid dehydrogenase type 1 have been shown recently to ameliorate cardiovascular risk factors and inhibit the development of atherosclerosis. (Hadoke, Iqbal et al. 2009)

There is also promising studies that indicate inhibition ameliorates metabolic syndrome and prevents progression of atherosclerosis in mice. (Hermanowski-Vosatka, Balkovec et al. 2005) (Lloyd, Helmering et al. 2009)

Metabolic Syndrome

Inhibition of 11 β -HSD is currently being explored to control metabolic syndrome. (Morton and Seckl 2008; Morton 2009)

One study found 11beta-HSD1 expression in lean women was found to be significantly lower than in lean males. The up-regulation associated with obesity may be relatively more devastating in women than in men, and may help explain the higher relative risk of cardiovascular disease in women suffering from the metabolic syndrome. (Paulsen, Pedersen et al. 2007)

Inflammation

Glucocorticoids have an anti-inflammatory effect. In general, 11 β -HSD1 expression is increased and 11 β -HSD2 decreased by pro-inflammatory stimuli or during inflammation. (Chapman and Seckl 2008) (Chapman, Coutinho et al. 2009)

Colon Cancer

A recent study showed that inhibition of 11beta-hydroxysteroid dehydrogenase type II selectively blocks the tumor COX-2 pathway and suppresses colon carcinogenesis in mice and humans. (Zhang, Xu et al. 2009)

Osteoporosis

Urinary measures of 11beta-HSD1 activity predict the response of bone formation markers to glucocorticoids, and this appears to reflect increased generation of active glucocorticoids within osteoblasts. (Cooper, Blumsohn et al. 2003) (Cooper 2008)

Glaucoma

One study found that inhibition of 11beta-hydroxysteroid dehydrogenase type 1 lowers intraocular pressure in patients with ocular hypertension. (Rauz, Cheung et al. 2003)

One study found that primary open-angle glaucoma exhibit increased peripheral vascular sensitivity to glucocorticoids. Patients with primary open-angle glaucoma exhibited a greater cutaneous vasoconstrictor response to glucocorticoids than patients with ocular hypertension and normal subjects (20.7 +/- 3.1 vs. 8.5 +/- 4.4 and 8.6 +/- 4.5 arbitrary units, respectively; P < 0.05 in each case). (Stokes, Walker et al. 2003)

Polycystic Ovary Syndrome

One study found that lean polycystic ovary syndrome had (among other endocrine/hormonal abnormalities) reduced 11beta-HSD1 activities when compared with lean controls. (Tsilchorozidou, Honour et al. 2003)

An earlier study found no relationship. (Chin, Shackleton et al. 2000)

Therapies

Diet

Preliminary research shows that diets high in fat or simple carbohydrates affect 11beta-HSD in ways that promote obesity. (London and Castonguay 2009)

Sucrose and Fructose

One study showed that sucrose can promote increased 11beta-HSD-1 and hexose-6-phosphate dehydrogenase message in mesenteric fat while concomitantly decreasing 11beta-HSD-1 message and increasing exose-6-phosphate dehydrogenase message in liver. (London, Lala et al. 2007)

Fructose-6-phosphate increased the activity of 11beta-HSD1 reductase (McCormick, Wang et al. 2008)

NADPH

Reduced NADPH is a co-factor for 11beta-HSD-1. (Agarwal 2003)

11beta-HSD1 acts predominantly as an oxoreductase using NADP(H) as a cofactor to generate cortisol, whereas 11beta-HSD2 acts exclusively as an NAD-dependent dehydrogenase, inactivating cortisol to cortisone. (Walker and Stewart 2003)

DHEA

One study showed that DHEA induces a shift from 11beta-HSD1 to 11beta-HSD2 expression, increasing conversion from active to inactive glucocorticoids. (Balazs, Schweizer et al. 2008)

Licorice

18beta-glycyrrhetic acid (GA), a metabolite of the natural product glycyrrhizin, is not selective and inhibits both 11beta-HSD1 and 11beta-HSD2. 18alpha-GA selectively inhibits 11beta-HSD1 but not 11beta-HSD2. This is in contrast to 18beta-GA, which preferentially inhibits 11beta-HSD2. (Classen-Houben, Schuster et al. 2009)

Inhibition of 11 beta-dehydrogenase after licorice ingestion results in cortisol acting as a potent mineralocorticoid. (Stewart, Wallace et al. 1990)

A study published in *Lancet* showed that in seven normal subjects given licorice, sodium retention is associated with a significant change in cortisol metabolism indicating inhibition of 11-beta-hydroxysteroid dehydrogenase. (Stewart, Wallace et al. 1987)

Glycyrrhizic acid (glycyrrhetic acid glucuronide), when given orally to rats, partially inhibited renal 11 beta-dehydrogenase. (Monder, Stewart et al. 1989)

A recent article warns that licorice is contraindicated in patients with a 11β-HSD type 2 mutation. (Harahap, Sasaki et al. 2009)

Vitamin D3

One study found that cortisol production was dose dependently augmented (2- to 6-fold, $p < 0.001$) by 1,25-dihydroxyvitamin D3 (0.1 to 10 nM). 1,25-Dihydroxyvitamin D3 dose dependently increased 11beta-HSD 1 expression up to 2-fold ($p < 0.01$). (Morris and Zemel 2005)

Vitamin A

One study showed that retinoic acid (vitamin A) stimulates the expression of 11beta-hydroxysteroid dehydrogenase type 2. (Tremblay, Hardy et al. 1999) (Aubry and Odermatt 2009)

Glutathione

One study found that oxidized glutathione (GSSG) attenuated 11beta-HSD1 reductase activity by 40% while reduced glutathione (GSH) activated the reductase in liver. Fat microsomes were unaffected because they lack glutathione reductase. (McCormick, Wang et al. 2008)

Cadmium and Lead

Cadmium, a common environmental pollutant and a major constituent of tobacco smoke, has been identified as a new class of endocrine disruptors with a wide range of detrimental effects on mammalian reproduction. During human pregnancy, maternal cadmium exposure, via the environment and/or cigarette smoking, leads to fetal growth restriction (FGR). One study showed that cadmium reduces human placental 11 beta-HSD2 expression and activity by suppressing HSD11B2 gene transcription. (Yang, Julan et al. 2006)

17-beta-Hydroxysteroid dehydrogenase was reduced to 33%, 38%, and 24% on treatment of lead, cadmium, and co-exposure (Pb + Cd)(Pandya, Pillai et al. 2009)

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 diallyl sulfide (DAS), a sulfur-containing volatile compound present in garlic, 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)

Estradiol

One article proposed that inhibition of 11β-HSD type 1 by estradiol is an explanation for the detrimental effects of postmenopausal hormone replacement therapy. (Cohen 2005)

A recent article showed that 17Beta-estradiol inhibits 11beta-hydroxysteroid dehydrogenase type 1 activity in rodent adipocytes. The authors propose that this provides a novel insight into the anti-obesity mechanism of estrogen. (Tagawa, Yuda et al. 2009)

Growth Hormone and Insulin-like Growth Factor

One study found that growth hormone (GH) and/or insulin-like growth factor (IGF) inhibits 11β-HSD type 1. Thus, GH deficiency effectively increases cortisol production in key target tissues

including liver and adipose tissue, promoting insulin resistance and visceral adiposity. (Stewart, Toogood et al. 2001) (Agha and Monson 2007)

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