Chapter 16
The Dehydrogenase Hypothesis

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Abstract Circulating glucocorticoid (GC) levels are controlled by the Hypothalamo–Pituitary–Adrenal (HPA) axis, but within tissues, GC availability is controlled by the isoforms of 11β (Beta)-Hydroxysteroid Dehydrogenase 11β (Beta)-HSD that interconvert inactive cortisone and active cortisol. Two isoforms have been identified; in key metabolic target tissues (including liver and adipose), expression of 11β (Beta)-HSD1 predominates that *in vivo* converts cortisone to cortisol and thus amplifies local GC action. In contrast, in mineralocorticoid target tissues 11β (Beta)-HSD2 is the isoform that is most abundantly expressed. This inactivates cortisol to cortisone and offers protection for the mineralocorticoid receptor form occupation and activation by cortisol. Dysregulated 11β (Beta)-HSD1 activity has been implicated in many metabolic diseases such as obesity and diabetes and inhibition of 11β (Beta)-HSD1 represents a promising therapeutic target. Mutations within the gene encoding 11β (Beta)-HSD2 cause the Syndrome of Apparent Mineralocorticoid Excess and decreases in activity are linked to hypertension as well as impairment in placental function and neonatal growth. We will discuss the molecular biology and enzymology of 11β (Beta)-HSD and its role in normal physiology and discuss altered 11β (Beta)-HSD activity in pathological states and the potential for therapeutic targeting.

Keywords 11β (Beta)-HSD • Endoplasmic reticulum (ER) • Cortisol • Cortisone • H6PDH • NADPH

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Introduction

Glucocorticoids (GC) (cortisol in man and corticosterone in rodents) are crucial in regulating many important physiological functions including glucose and amino acid metabolism, inflammation, immunity and general health and well-being [1]. GCs bind to the glucocorticoid receptor (GR), a member of the nuclear receptor family and alter gene transcription up-regulating anti-inflammatory protein synthesis and reducing expression of pro-inflammatory cytokines.

Since their discovery in the 1940s by Kendall and Hench, GCs have become a mainstay of therapy in many clinical conditions including rheumatoid arthritis, asthma and as a cornerstone in anti-rejection medication regimes in organ transplant recipients.

Whereas circulating GC levels are regulated by the Hypothalamo–pituitary–adrenal (HPA) axis, tissue cortisol metabolism is under the control of the enzymes of the 11β (Beta)-Hydroxysteroid Dehydrogenase (11β (Beta)-HSD) system. Two isozymes exist, namely 11β (Beta)-HSD1 and 11β (Beta)-HSD2. In recent decades, attention has focussed on tissue cortisol metabolism and the pre-receptor regulation of GCs within tissues such as fat, muscle and liver [2–6]. 11β (Beta)-HSD1 is a bi-directional enzyme, which *in vivo* acts primarily as an oxo-reductase, converting inactive cortisone (and inactive 11-dehydrocorticosterone in rodents) to active cortisol. 11β (Beta)-HSD1 is located in a number of key metabolic tissues including liver, skeletal muscle, gonads and adipose tissue [6, 7] and has key metabolic influence acting as an amplification step in tissue cortisol exposure. Tissue exposure to GC therefore is not only reliant on circulating levels of cortisol but can also be altered by pre receptor regulation via 11β (Beta)-HSD1. Dysregulated 11β (Beta)-HSD1 activity has recently been implicated in many metabolic and inflammatory diseases and is a promising target to alter tissue glucocorticoid exposure. Selective 11β (Beta)-HSD1 inhibitors exist and have been trialled in early phase 2 studies primarily in type 2 diabetes [8].

11β (Beta)-HSD2 is expressed in aldosterone selective tissues, mainly in the distal nephrons, colonic epithelium, salivary and sweat glands (mineralocorticoid receptor (MR) expressing tissues) and in the foetus and placenta during gestation. It acts uniquely as a dehydrogenase deactivating cortisol to inactive cortisone, protecting tissues from excess glucocorticoid exposure [6, 9]. 11β (Beta)-HSD2 deficiency or inhibition causes hypertension secondary to apparent mineralocorticoid excess whereby cortisol activates the MR for which it shares the same affinity as aldosterone. A similar syndrome manifests in people ingesting large amounts of European licorice which contains an inhibitor of this enzyme. 11β (Beta)-HSD2 is important in gestation with significant activity in both placenta and fetal brain development by preventing early exposure to GCs.

Hypothalamic Pituitary Adrenal Axis and Cortisol Production

GCs, synthesized from cholesterol precursors, are produced primarily by the adrenal cortex (zona fasiculata) under the influence of the HPA axis in a classical circadian rhythm, regulated by negative feedback.

Healthy adults secrete 10–15 mg s cortisol/day [10]. The majority of cortisol is protein bound to cortisol binding globulin (CBG) although some is albumin bound. Estimates suggest that only 5 % of circulating cortisol is "free" and biologically active [11, 12]. The half-life of free cortisol is only a few minutes whereas protein bound cortisol has a much longer half life of between 70 and 120 min [11, 13, 14]. Cortisone has similar unbound concentrations to that of cortisol but has a lower affinity for both CBG and GR [12, 15]. Importantly the biological availability of GCs represents a balance between synthesis/secretion and metabolism/clearance.

Cortisol Metabolism and Clearance

There are multiple pathways involved in cortisol and cortisone metabolism. These include A-ring reduction to from tetrahydrocortisol and it's 5α (alpha)-isomer allo-tetrahydrocortisol, hydroxylation to 6β (Beta) hydroxycortisol and reduction of the 20-oxo group giving cortols. Among the various distinct pathways, perhaps the most critical of these is the inter-conversion of cortisol and cortisone mediated by the 11β (Beta)-HSD isozymes. 11β (Beta)-HSD interconverts cortisol and cortisone by altering the hydroxyl group at C11 (see Fig. 16.1).

Tissue Cortisol Metabolism: 11β (Beta) HSD1

11β (Beta) HSD1: Discovery

Glucocorticoids were discovered in the 1940s and 1950s and were heralded as a potentially curative treatment for many ailments [16]. Kendall et al. published the discovery of what they believed to be a treatment that could reverse rheumatoid arthritis in the 1950s [17]. What they referred to as Compound E; was actually cortisone, a

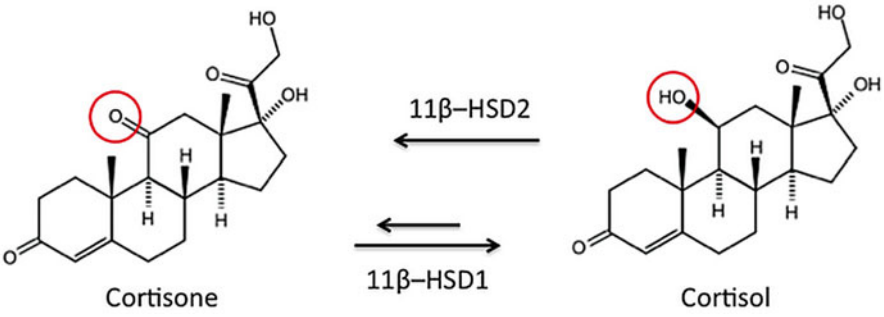

Fig. 16.1 Isoforms of 11β (Beta)-Hydroxysteroid dehydrogenase as pre-receptor regulators of glucocorticoid availability

precursor of cortisol (Compound F). We now know that the cortisone administered, was converted to cortisol by 11β (Beta)-HSD1. The hydroxyl group at C11 is crucially important for cortisol to be effective. 11β (Beta)-HSD1 reduces inactive cortisone to active cortisol by adding a hydroxyl group at C11. Thus, unbeknownst to the authors they had actually made two discoveries—the first that the glucocorticoid cortisol has dramatic therapeutic effect on arthritis and second that the enzyme 11β (Beta)-HSD1 has the ability to convert inactive cortisone to active steroid.

Subsequently to Kendall's paper, cortisol, and not cortisone, was established as the active steroid. It also became apparent that inter-conversion between cortisone and cortisol is possible [18, 19]. This conversion is made possible by the enzyme 11β (Beta)-HSD1, a member of the dehydrogenase/reductase superfamily. Short-chain Dehydrogenase/Reducatse (SDR) enzymes are NADP(H) dependent enzymes, that are involved primarily in breaking down hormones and chemical messengers [20]. There are more than 3,000 members in the SDR family [7].

Early studies identified 11β (Beta)-HSD activity in different tissues such as placenta, kidney and liver. However, 11β (Beta)-HSD did not have the same activity between different tissues. The "set point" of the enzyme varied from tissue to tissue with dehydrogenase activity (cortisol conversion to cortisone) predominating in the placenta and kidney and reductive activity (cortisone conversion to cortisol) predominating in liver [7]. The answer lay in the fact that there are two distinct isozymes of 11β (Beta)-HSD namely type 1 being predominantly reductive and type 2 acting solely as a dehydrogenase. In addition 11β (Beta)-HSD type 1 is a bi-directional capable of acting in either direction but dependent on co-factors such as NADPH. *In vivo* in intact tissues the 11β (Beta)-HSD1 enzyme acts as an oxo-reductase converting cortisone to cortisol. Purified 11β (Beta)-HSD1 enzyme behaves principally as a dehydrogenase, oxidizing cortisol to cortisone.

Human 11β (Beta)-HSD1

11β (Beta)-HSD1 was initially purified and cloned from rodents in the 1980s by Carl Monder's group [21, 22]. In humans the gene for 11β (Beta)-HSD1 (HSD11B1) is located on chromosome 1, is 30 kb in length and has six exons and five introns. It comprises of 292 amino acids and shares 77 % homology with rat amino acid sequence [23]. Human 11β (Beta)-HSD1, cloned in 2002 [24], exits as a dimer [25] and is bound to the endoplasmic reticulum (ER) with its catalytic domain within the ER lumen [26] (see Fig. 16.2). The catalytic directionality of the enzyme is based on the position of 11β (Beta)-HSD1 within the ER lumen where it co-localises with Hexose 6 Phosphate Dehydrogenase (H6PD). H6PD generates the reduced co-substrate NADPH. Thus the ratio of NADPH/NADP confers directionality to 11β (Beta)-HSD1 [27, 28]. Purified 11β (Beta)-HSD1, in the absence of H6PD, behaves principally as a dehydrogenase, oxidizing cortisol to cortisone. The enzyme 11β (Beta)-HSD1, has Michaelis Menten (K_m) constants of 1.83 ± 0.06 μm for corticosterone and 17.3 ± 2.2406 μm for cortisol [7].

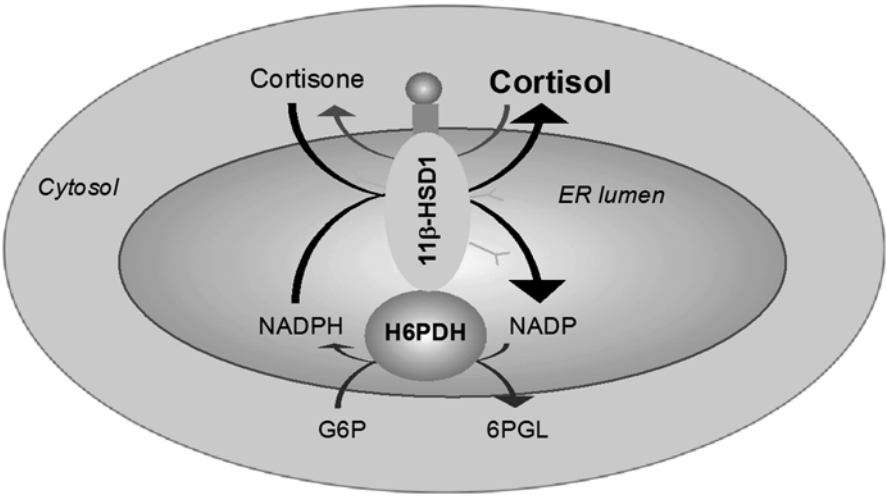

Fig. 16.2 Localization and co-factor dependency of 11β (Beta)-HSD1 within the endoplasmic reticulum

11β (Beta)-HSD1 Ontogeny

The ontogeny of 11β (Beta)-HSD1 has been studied predominantly in rodents and sheep animal models. The expression of mammalian 11β (Beta)-HSD1 is predominantly post-natal. In general 11β (Beta)-HSD1 is detectable in many tissues but there is a lack of activity in early gestation with reductase activity only becoming apparent after delivery and rising steadily throughout infancy [7, 29]. The ontogeny of 11β (Beta)-HSD1 in humans is not well documented with few published studies. Cortisone therapy is not useful for treating congenital adrenal hyperplasia in early infancy most likely due to absent or significantly reduced liver 11β (Beta)-HSD1 activity [30]. Both reductase and dehydrogenase activity has been demonstrated in fetal lung tissue [31, 32]. 11β (Beta)-HSD1 activity remains unchanged throughout childhood in both boys and girls [33]. At puberty there is a reduction in 11β (Beta)-HSD1 activity in women [33] and this appears to remain. In adults, there is a well described dimorphism in cortisol metabolism between men and women with an apparent reduction in 11β (Beta)-HSD1 activity in women [34, 35]. However, not all studies have shown this dimorphism [36].

Regulation of 11β (Beta)-HSD1 Expression

11β (Beta)-HSD1 expression increases steadily until 1 year of age at which time peak levels are reached. 11β (Beta)-HSD1 is expressed in many tissues including liver, adipose tissue, gonads, GI tract, kidney, eye, anterior pituitary, leukocytes and

bone [7]. 11β (Beta)-HSD1 expression is highest in liver, brain gonads and adipose tissues [37]. Many factors contribute to alterations in tissue expression of 11β (Beta)-HSD1. In general glucocorticoids, pro-inflammatory cytokines (TNFα, IL-1β) peroxisome proliferator-activated receptor γ agonists and CEBPs increase 11β (Beta)-HSD1 expression whereas Growth Hormone (GH) and liver X receptor agonists inhibit 11β (Beta)-HSD1 expression [7]. Recently salicylates have been shown to down regulate 11β (Beta)-HSD1 expression [38] in adipose tissue and improve insulin sensitivity. The effects of sex steroids, insulin and other hormones are variable across tissues and between species. 11β (Beta)-HSD1 has been shown to be expressed more in adipose tissue in lean women compared to lean men [39]. High dose oestradiol has been shown to repress 11β (Beta)-HSD1 expression in rat liver and kidney but testosterone did not alter expression [40].

Tissue-Specific Role of 11β (Beta)-HSD1

Adipose Tissue

11β (Beta)-HSD1 is highly expressed in human adipose tissue [3, 41]. Broadly speaking, studies have shown similar expression levels of 11β (Beta)-HSD1 between visceral and subcutaneous compartments [39, 42, 43]. However, H6PD and GR have been shown to have different levels of expression between adipose tissue depots [43].

As in other tissues, 11β (Beta)-HSD1 acts primarily as a reductase generating active GCs. Its expression and activity are induced by GCs and inflammatory cytokines such as interleukin 1 and TNFα [7, 44–47]. 11β (Beta)-HSD1 expression and activity increases upon adipocyte differentiation [48] and inhibition of 11β (Beta)-HSD1 blocks cortisone-induced adipocyte differentiation [49]. 11β (Beta)-HSD1 activity within adipose tissue depots is controversial with some studies demonstrating increased activity in omental tissue compared to subcutaneous adipose tissue.

Dysregulation of 11β (Beta)-HSD1 activity has been postulated to be critical in the pathogenesis of metabolic complications associated with obesity. In rodent models increased 11β (Beta)-HSD1 activity has been demonstrated in visceral adipose tissue of obese rodents compared to wild type [50, 51] although expression in adipose tissue was reduced following high fat feeding in mice [52]. Short term high fat diet reduced the activity of 11β (Beta)-HSD1 in both subcutaneous and visceral adipose tissue in Wistar rats [53]. Genetically modified rodent models have contributed significantly to our understanding of the role of 11β (Beta)-HSD1 in adipose tissue. 11β (Beta)-HSD1 knockout mice are resistant to the metabolic side effects of a high fat diet compared to wild type [54]. Conversely over expression of 11β (Beta)-HSD1 in adipose tissue leads to weight gain and metabolic complications compared to wild type [55] even on a chow diet.

Clinical studies have yielded varied and sometimes conflicting results. In human adipose tissue, the majority of studies have examined subcutaneous adipose tissue. 11β (Beta)-HSD1 activity in subcutaneous adipose tissue has been shown to be

increased in obese patients compared to non-obese controls [56]. Both 11β (Beta)-HSD1 activity and expression were shown to correlate positively with BMI by Lindsay et al. in 2003 [57]. Whilst the majority of studies show a positive relationship of 11β (Beta)-HSD1 expression and activity with BMI, this is not the case for all studies. Data with regards to the omental depot are more sparse, but some studies have identified increased expression in women in association with increased omental adiposity [58]. The impact of diet induced obesity on 11β (Beta)-HSD1 activity and expression is not clear. Obese Zucker rats have increased visceral adipose tissue 11β (Beta)-HSD1 expression compared to lean rats [51] however Wistar rats, fed a short term high fat diet show reduced 11β (Beta)-HSD1 activity [53]. Diet induced obese mice also have reduced expression of 11β (Beta)-HSD1 [59]. In these diet induced obese mice 11β (Beta)-HSD1 expression is increased by NFκ (Kappa) B and reduced by HIF-1. H6PD is also important in the directionality of 11β (Beta)-HSD1 and some studies suggest a role in visceral adipose tissue [60]. Pro inflammatory cytokines and glucocorticoids (increased in obesity) are also known to induce 11β (Beta)-HSD1 expression in adipose tissue [7]. In vitro studies highlight the role of transcription factors (CEBPs) for controlling 11β (Beta)-HSD1 expression in adipocytes [61, 62].

Liver

GCs have key metabolic effects on the liver, augmenting insulin stimulated lipogenesis [63] and reducing lipolysis in hepatic tissue [64]. Indirectly, they increase hepatic lipid accumulation by inducing surrounding adipose tissue lipolysis thus increasing the delivery of free fatty acids to the liver via the portal circulation [65].

11β (Beta)-HSD1 expression and activity has been extensively studied in hepatic tissue. In animal studies global 11β (Beta)-HSD1 knock out mice are protected from diet induced hepatic steatosis when fed a high fat diet [54, 55]. Transgenic mice with hepatic 11β (Beta)-HSD1 overexpression, develop hypertension, hepatic steatosis and dyslipidemia but interestingly do not develop steatohepatitis and minimal insulin resistance [66]. Other factors including HPA axis activation and adipose tissue 11β (Beta)-HSD1 activity may play a role in the development of hepatosteatitis. Liver specific HSD1-null mice have minimal phenotype (ref) suggesting visceral adipose HSD1 is the key site of action and excess adipose-generated GCs act on the liver via visceral portal drainage.

11β (Beta)-HSD1 is highly expressed in human liver [23], predominantly in a centripetal pattern histologically with maximum expression around the central vein [67]. Hepatic 11β (Beta)-HSD1 appears to act exclusively as an oxo-reductase generating active GC [68]. In animal rodent models over expression of 11β (Beta)-HSD1 in visceral adipose tissue was associated with Non Alcoholic Fatty Liver Disease (NAFLD) [69]. In humans, some studies have demonstrated increased expression of 11β (Beta)-HSD1 in liver tissue in obese persons with metabolic syndrome [70] however other studies have not confirmed these findings [71, 72]. Liver 11β (Beta)-HSD1 activity, as measured by urinary steroid metabolite analysis is reduced in obesity compared to non-obese controls [73]. Liver 11β (Beta)-HSD1 activity (using serum cortisol generation form oral cortisone) is also reduced in

obesity compared to non-obese controls [73]. These reductions in both liver 11β (Beta)-HSD1 activity and expression contrast with increased activity and expression in adipose tissue in obesity. Ahmed et al. have described a switch in the expression of 11β (Beta)-HSD1 across the spectrum of liver disease from lower expression of 11β (Beta)-HSD1 in steatosis to higher levels of 11β (Beta)-HSD1 expression associated with steatohepatitis [74]. The authors concluded these changes might reflect a response to a more inflammatory phenotype.

Skeletal Muscle

GCs play an important role in protein metabolism. In Cushing's syndrome the effect of excess GCs is clearly seen with myopathy and muscle atrophy. 11β (Beta)-HSD1 is expressed in skeletal muscle [75, 76], whereas 11β (Beta)-HSD2 is not. 11β (Beta)-HSD1 activity has been demonstrated in skeletal muscle [77] and it may have a role in insulin sensitivity and metabolic disease. Increased expression [78] and activity [79] have been demonstrated in rats and humans with type 2 DM.

The exact role of 11β (Beta)-HSD1 in sarcopaenia remains unexplained. It is thought that increased 11β (Beta)-HSD1 activity may play a role in allowing increased muscle cortisol exposure. Increased 11β (Beta)-HSD1 expression in skeletal muscle is associated with reduced muscle strength in older adults compared to younger controls [80].

Skin

Data on tissue cortisol metabolism within skin is only recently becoming an area of interest and investigation. Skin has been shown to be an active site of cortisol production and metabolism [81, 82]. Excess skin exposure to GC's cause skin changes similar to the natural aging process. These include reduced elasticity, reduced collagen and fibroblast numbers, thinning of dermis and epidermis and a general reduction in the repair capacity of skin [83]. Increased exposure to GC's has been postulated as a factor in age related changes, inflammatory and auto-immunity changes seen in skin [84]. It has been postulated that skin changes seen over time are in part as a result of 11β (Beta)-HSD1 activity [82].

Both 11β (Beta)-HSD1 and 2 are expressed in skin [81, 82, 85]. 11β (Beta)-HSD2 is expressed in association with the mineralocorticoid receptor on sweat glands however its role (if any) within the dermis and epidermis is debated. In wound healing, 11β (Beta)-HSD2 expression has been shown to be induced 48 h after tissue injury with subsequent return to basal levels at 96 h [81]. This has been postulated to be a mechanism to reduce local cortisol excess following inflammation.

11β (Beta)-HSD1 is widely expressed in human and mouse dermis and epidermis [82, 85, 86]. Upon differentiation of keratinocytes 11β (Beta)-HSD1 expression increases [85], somewhat akin to the changes seen with pre adipocyte differentiation [87]. Interestingly despite reducing levels of expression of 11β (Beta)-HSD1 in

elderly subjects, a paradoxical rise in 11β (Beta)-HSD1 activity is seen with increasing age in both humans and mice [82]. This gives credence to the concept of age related skin atrophic changes being in part due to increased cortisol exposure secondary to increased 11β (Beta)-HSD1 activity.

11β (Beta)-HSD1 has been shown to have a pivotal role in skin repair following injury [88] and tissue remodeling [85]. In mice 11β (Beta)-HSD1 is contributory to impaired wound healing. Blocking 11β (Beta)-HSD1 improved wound healing in mice and prevented age induced skin changes [89]. These data suggest that 11β (Beta)-HSD1 generated local cortisol is critically important in wound healing and in aging skin changes. Inhibitors of 11β (Beta)-HSD1 inhibitors (topical or oral) may therefore have therapeutic potential.

Cardiovascular System

Both isozymes are expressed in blood vessel walls [90] and heart [91], however oxo reductase directionality (11β (Beta)-HSD1) predominates in vascular smooth muscle [88]. There is evidence linking 11β (Beta)-HSD1 activity with atherosclerosis. Mediastinal adipose tissue 11β (Beta)-HSD1 has been linked with coronary atherosclerosis [92]. The same authors demonstrated increased 11β (Beta)-HSD1 expression in aortas of obese patients with the metabolic syndrome [93]. 11β (Beta)-HSD1 inhibition in apoE knockout mice achieved significant reduction atherosclerotic load suggesting a role in plaque formation [94]. Carbenoxolone treatment has been shown to reduce atherosclerosis in mice [95]. 11β (Beta)-HSD1 knock out mice show improved angiogenesis to infarcted regions possibly through reduced GC regeneration locally [96].

Central Nervous System (CNS)

GCs are required for normal brain development and normal brain function. Excess GCs are associated with alterations in mood, memory and brain function [97, 98]. Both 11β (Beta)-HSD1 and 2 are expressed in the brain [99–102], but 11β (Beta)-HSD2 is expressed at lower levels. 11β (Beta)-HSD1 acts principally as an oxo-reductase in brain tissue [103] but interestingly H6PD does not always co-localise with 11β (Beta)-HSD1 in the CNS [101]. This lack of universal co-localisation suggests other enzymes providing the necessary co factors for 11β (Beta)-HSD1. Elevated 11β (Beta)-HSD1 is seen with ageing and is associated with cognitive decline. Altered 11β (Beta)-HSD1 activity in the CNS is associated with changes in appetite, affective behavior and circadian rhythm [104].

A putative role for 11β (Beta)-HSD1 in cognitive impairment is postulated along with investigations looking at the link between 11β (Beta)-HSD1 and human eye disease including thyroid eye disease [105] and glaucoma. 11β (Beta)-HSD1 inhibitors have been shown to improve cognitive function in elderly persons with T2 DM [106].

Inflammation and Immunity

Glucocorticoids in pharmacological doses are immunosuppressive and produce powerful anti-inflammatory effects [107]. They achieve this by altering gene transcription and altering pro and anti-inflammatory mediators including cytokines and signaling pathways. 11β (Beta)–HSD1 is believed to play a key role in local inflammation and immune response to stimuli and allergens [108].

11β (Beta)-HSD1 is expressed on numerous immune cell types in humans including mast cells, mononuclear cells and macrophages, lymphocytes, B cells and dendritic cells [109–112]. 11β (Beta)-HSD1 is not expressed in non-stimulated monocytes but 11β (Beta)-HSD1 expression is increased upon differentiation of monocytes cells into macrophages with interleukin 4 and 13 [110]. A further increase in 11β (Beta)–HSD1 expression is seen when monocytes differentiate into dendritic cells under the influence of interleukin-4 and granulocyte-macrophage colony-stimulating factor. Other pro-inflammatory cytokines do not increase 11β (Beta)-HSD1. In macrophages, 11β (Beta)-HSD1 activity increases with exposure to lipopolysaccharide [110]. 11β (Beta)-HSD1 expression has also been seen in murine lymphocytes and B cells with increases seen when CD4-positive lymphocytes polarize into Th1 or Th2 subsets [111].

Separate to expression, the functional role of 11β (Beta)-HSD1 in immunity remains debated as it is difficult to separate out the specific subsets of immune cells and to be confident of the role (if any) of 11β (Beta)-HSD1. Our understanding of 11β (Beta)-HSD1 expression and activity on human immune cell actions and inflammation is incomplete and warrants further investigation.

There is evidence both in animal models and in human studies that demonstrate that 11β (Beta)-HSD1 is implicated in immune response to infection and inflammation. In 11β (Beta)-HSD1 knock out mice defective macrophage phagocytosis of apoptotic neutrophils is seen in peritonitis [113]. KO mice have increased susceptibility to endotoxaemia compared to wild type [114]. Of note, a study in mice demonstrated that in various models of joint and lung inflammation 11β (Beta)-HSD1 knock out mice developed inflammation earlier, substantially more inflammation and slower resolution of inflammation compared to wild type controls [115]. This study suggests that 11β (Beta)-HSD1 plays a key role as an anti-inflammatory regulator and raises concerns for drug therapy inhibiting 11β (Beta)-HSD1.

In humans (and rats) 11β (Beta)-HSD1 expression is elevated in colitis [116, 117] with a concomitant reduction in 11β (Beta)-HSD2 expression. Acute exacerbations of inflammatory bowel disease are associated with elevated 11β (Beta)-HSD1 expression [118] but interestingly 11β (Beta)-HSD1 activity was elevated in patients who were in remission, suggesting that high local glucocorticoid levels are important in limiting inflammation. In a rat model, chemically induced inflammation increased 11β (Beta)-HSD1 expression both in colonic tissue and lymphoid tissue [119].

Recently, 11β (Beta)-HSD1 has been shown to provide tonic inhibition of mast cell deactivation. 11β (Beta)-HSD1 knock out mice had increased mast cell numbers and a lower threshold for deactivation suggesting that reduced 11β (Beta)-HSD1 activity increases allergy and anaphylaxis [109].

Bone and Joint

11β (Beta)-HSD1 is expressed in human bone [120], predominantly in osteoblasts [121].

In rheumatoid arthritis, both 11β (Beta)-HSD1 and 11β (Beta)-HSD2 isozymes are expressed in synovial tissue with conflicting reports as to which is the dominant isoform. Global 11β (Beta)-HSD1 activity is increased in rheumatoid arthritis (as measured by urinary corticosteroid metabolites) compared to non-arthritic controls [122]. Enzyme activity correlates with synovial inflammation severity [123]. In animal models 11β (Beta)-HSD1 knock out mice develop more severe arthritis and earlier compared to wild type controls [115]and mice treated with 11β (Beta)-HSD1 inhibitors (Carbenoxolone) developed worse arthritis [124].

Cortisone Reductase Deficiency (CRD) and Apparent Cortisone Reductase Deficiency (ACRD)

Genetic defects in both HSDB1 and H6PD encoding genes demonstrate the effect of alterations in tissue 11β (Beta)-HSD1 on clinical phenotype. Both Cortisone Reductase Deficiency (CRD) from HSDB1 gene defects and apparent Cortisone Reductase Deficiency (ACRD) from H6PD gene defects show the impact of reduction in tissue 11β (Beta)-HSD1 activity with low urine cortisol, significantly elevated cortisone with subsequent compensatory increased HPA activity leading to hyperandrogenism, early adrenarche and PCOS in women [7, 125].

CRD was first described in the 1980s. The majority of cases are female and present with clinical and biochemical hyperandrogenism, with males presenting with precocious puberty [7, 37]. CRD has been described as the "human 11β (Beta)-HSD1 knockout" [7]. The condition is ameliorable to dexamethasone therapy. It shares some clinical and biochemical features and should not be confused with non-classical congenital adrenal hyperplasia.

11β (Beta)-HSD1 Inhibition in Clinical Studies

Due to evidence that has implicated 11β (Beta)-HSD1 in the pathogenesis of disease states including obesity, diabetes and the metabolic syndrome, it represents an exciting therapeutic target to limit local GC availability [2, 126]. Many inhibitors of the 11β (Beta)-HSD enzymes have been described. These include naturally occurring inhibitor compounds such as liquorice derived glycyrrhetinic acid [127], flavanone/hydroxyl flavanones [128], bile acids [129], progesterone metabolites [130] and even coffee [131]. Most of these naturally occurring compounds inhibit both 11β (Beta)-HSD1 and 11β (Beta)-HSD2, with subsequent hypertension and hypokalaemia limiting their possible benefits.

Carbenoxolone, a non-selective inhibitor derived from glycyrrhetinic acid, was the first drug to show benefit in human studies [4, 132]. In healthy volunteers it

improved insulin sensitivity and reduced glucose production rates via a reduction in glycogenolysis but not gluconeogenesis in patients with type 2 diabetes [132]. Carbenoxolone has also been shown to reduce local cortisol availability in subcutaneous adipose tissue and inhibits glucocorticoid induced lipolysis [4]. These early small "proof of principal" studies demonstrated that 11β (Beta)-HSD1 in metabolic disease could be targeted for drug manipulation and importantly that tissue specific effect could be demonstrated, despite a relative lack of specificity of carbenexolone on 11β (Beta)-HSD1. Several pharmaceutical companies have developed potent selective 11β (Beta)-HSD1 inhibitors. Indeed 11β (Beta)-HSD inhibition has become a significant area of investment for many companies [133] and an extensive array of chemical compounds have been patented and reviewed extensively elsewhere [134]. In general, they are highly selective for 11β (Beta)-HSD1 over 11β (Beta)-HSD2 and have high potency for inhibition.

A small number of clinical trials have been published with relatively short durations of intervention (all no more than 12 weeks) and have demonstrated improvements in biomarkers including cholesterol profiles, weight, glycaemic control and blood pressure [8, 135, 136]. The first outcome study to be published investigated the addition of an 11β (Beta)-HSD1 inhibitor (INCN13739) to metformin in patients with type 2 Diabetes. The drug was well tolerated and the 12 week study demonstrated improvements in weight, glycaemic control and lipid profiles in those people that received the inhibitor [135]. Of note, in this trial there was a compensatory increase in the HPA axis with a dose dependent increase in ACTH and subsequent increase in certain androgens. In women there was a small and significant increase in testosterone levels but biologically active testosterone was felt to be unchanged as sex hormone binding globulin also increased. Whilst all blood results remained in the normal reference range these alterations and small elevations in androgens from HPA activation will remain a clinical concern in the long term, especially for women.

In a further study using a different compound (MK0916) again in the setting of type 2 diabetes and metabolic syndrome, modest improvements in glycaemic control with no reduction in fasting glucose levels were seen [8]. Again however there was mild activation of HPA with elevations in adrenal androgen secretion. Overall, the long-term side effects of 11β (Beta)-HSD1 inhibition remain unknown and while the benefits may outweigh any side effects the possible disruption of HPA axis will remain a concern alongside the magnitude of the clinical response.

Tissue Cortisone Metabolism: 11β (Beta)-HSD2

11β (Beta)-HSD2 Discovery

In 1993, Seckl et al. isolated an enzyme with exclusive 11β (Beta)-HSD dehydrogenase activity from both human placenta and rat kidney [137]. In 1994, Krozoski et al. isolated human 11β (Beta)-HSD from human kidney [138], identical to the dehydrogenase enzyme found in placenta. This second enzyme was found to be distinct from

11β (Beta)-HSD1 and was called 11β (Beta)-HSD2 and is also a member of the SDR family [139]. Both 11β (Beta)-HSD1 and 11β (Beta)-HSD2 isozymes are members of the Short-Chain Dehydrogenase/Reductase (SDR) superfamily of enzymes, however each isozyme has a distinct gene sequence with exons found on different chromosomes. There is little similarity or overlap in sequence between isozymes (18 % identity), except for similar co-factor binding regions at the NH_2-terminal [6].

The human 11β (Beta)-HSD2 gene is located on chromosome 16, has 5 exons and is only 6 kbs in length [140]. Human 11β (Beta)-HSD2 measures 405 amino acids in length and has a molecular mass of 44 kDa [138]. It is also anchored to the ER and loses its dehydrogenase activity once removed from tissue membranes [141]. 11β (Beta)-HSD2 universally acts as a dehydrogenase across species [6] and has a Km for cortisol of 50–60 nM and 10–13 nM for cortisone [6, 142]. Mutations in 11β (Beta)-HSD2 leading to apparent mineralocorticoid excess (AME) and hypertension have been extensively reported [143–145].

11β (Beta)-HSD2 Ontogeny

11β (Beta)-HSD2 has an important role in fetal development with intra uterine "programming" affecting subsequent adult physiology. 11β (Beta)-HSD2 plays an important role in gestation in humans and mammals protecting tissues against GC exposure prematurely. 11β (Beta)-HSD2 is expressed and active in placenta [36, 51] and steadily rises throughout gestation and declines 2 weeks prior to labour [29, 137, 146]. Placenta 11β (Beta)-HSD2 is localized to the syncytiotrophoblast where it has been described as a barrier to maternal corticosteroid which is considerably more concentrated [6]. GCs play a critical role in the development of fetal organs, in particular, towards the end of pregnancy, in lung tissue. Excess GC exposure in utero is associated with physiological and metabolic complications [147–149]. There is mounting evidence that 11β (Beta)-HSD2 plays a key protective role in normal development of the fetus and in particular brain development [148]. Altered or disrupted 11β (Beta)-HSD2 activity with subsequent excess intra-uterine exposure to glucocorticoid has a "programming" effect on the fetus leading to low birth weight and lifelong physiological consequences such as increased cardiovascular, metabolic and psychiatric complications [150]. This role in the development of the fetus and its role in subsequent lifelong physiology has led some to consider the degree of prenatal GC exposure as a potential prognostic biomarker [6].

Regulation 11β (Beta)-HSD2 Expression

Unlike 11β (Beta)-HSD1, there is considerable data published on the epigenetic influence on 11β (Beta)-HSD2 activity in humans and in rodent models.

The 11β (Beta)-HSD2 gene is susceptible to epigenetic influence, with methylation of the promoter region of particular interest. Increased methylation of this

region has been inversely associated with 11β (Beta)-HSD2 expression and influences the development of hypertension, intrauterine growth, birth weight and neurobehavioural movement [151, 152] in rats. Intrauterine growth retardation has been associated with increased methylation of 11β (Beta)-HSD2 gene promoter with subsequent repression of 11β (Beta)-HSD2 in adult kidneys [153].

Factors that increase 11β (Beta)-HSD1 expression tend to reduce 11β (Beta)-HSD2 such as TNFα [154]. Oestrogen increases 11β (Beta)-HSD2 expression [40, 155]. Vasopressin has been shown to stimulate 11β (Beta)-HSD2 [156]. Glucocorticoids down-regulate 11β (Beta)-HSD2 in foetal placenta but not foetal kidney [157]. Dexamethasone up-regulates 11β (Beta)-HSD2 in lung cells [158]. Hypoxia has been shown to reduce 11β (Beta)-HSD2 expression [159]. In colonic epithelium, aldosterone increases 11β (Beta)-HSD2 expression [160].

Tissue-Specific Role of 11β (Beta)-HSD2

CNS

In the adult brain, 11β (Beta)-HSD2 is expressed in a select few regions [161]. Before birth, 11β (Beta)-HSD2 is expressed in several additional brain regions, including the thalamus and cerebellum, where this enzyme protects proliferating granule cells from the growth-limiting effects of glucocorticosteroids [162, 163]. In adults, however, mRNA and protein are no longer detectable in these regions. Instead, 11β (Beta)-HSD2 expression is found in just a few small sites in adult mice and rats [161, 164] most prominently in a group of neurons found inside the nucleus of the solitary tract (NTS). NTS neurons with 11β (Beta)-HSD2 expression are the only cells in the brain shown to express both this enzyme and the mineralocorticoid receptor (MR); these "HSD2 neurons" are activated along with salt appetite after dietary sodium deprivation or volume depletion, and may trigger salt appetite. The only other brain sites in which 11β (Beta)-HSD2 expression (mRNA and protein) was identified consistently in adult animals are the subcommissural organ (a circumventricular organ comprised of modified ependymal cells which do not express MR) and a small subdivision of the ventromedial hypothalamic nucleus (neurons that lack MR immunolabeling). Information regarding 11β (Beta)-HSD2 expression remains incomplete for non-neuronal tissues such as the meninges, choroid plexus, ventricular ependyma, and cerebral vasculature.

Cardiovascular System

11β (Beta)-HSD2 is expressed in vascular endothelium [90]. 11β (Beta)-HSD2 knockout mice develop endothelial dysfunction [165]. Lack of 11β (Beta)-HSD2 and MR activation is implicated in generation of severe atherosclerosis in mouse models [166].

Kidney

11β (Beta)-HSD2 is perhaps best known for its role in the kidney where it protects the mineralocorticoid receptor from excess exposure to GC. 11β (Beta)-HSD2 is widely expressed in distal nephrons [141]. Although the inherent enzyme ability of 11β (Beta)-HSD2 to clear cortisol (converting it to cortisone) should not be enough, given concentrations and binding affinities, in reality it protects the mineralocorticoid receptor from GC exposure [6, 167]. Lack of 11β (Beta)-HSD2 in kidney (AME discussed below), leads to hypertension and other sequelae. 11β (Beta)-HSD2 activity, measured by urinary metabolite ratios, reduces with age suggesting a role in age related hypertension [168]. Some studies show a role of 11β (Beta)-HSD2 in hypertension although not all studies are in agreement [169]. In kidney disease reduced 11β (Beta)-HSD2 activity has been shown in persons with hypertension [170, 171].

Colon

11β (Beta)-HSD2 is expressed in colonic epithelium [172]. Expression is increased by aldosterone in rats [160]. In Inflammatory bowel disease 11β (Beta)-HSD2 expression is down regulated in both humans and rats [116]. This is accompanied by an increase in 11β (Beta)-HSD1 expression and so is presumed to be an attempt to locally control GC exposure to inflamed tissue. Zhang et al. showed that inhibiting 11β (Beta)-HSD2 reduces colon carcinogenesis by inhibiting COX 2 pathways. The reduction in 11β (Beta)-HSD2 blocked colorectal adenocarcinoma angiogenesis and metastasis [173].

Salivary Gland and Skin

As mineralocorticoid target tissues, both skin and salivary glands express 11β (Beta)-HSD2. In the skin expression is mainly restricted to sweat glands [174] 11β (Beta)-HSD2 is expressed in both parotid and sub-mandibular glands [174, 175]. Measuring salivary cortisone has been postulated a potential biomarker of serum free cortisol [176]. In addition, reduced activity of 11β (Beta)-HSD2 in sweat glands has also been linked with essential hypertension [177].

Pituitary

In normal anterior pituitary tissue 11β (Beta)-HSD2 mRNA expression is seen, but immunofluorescence reveals absent 11β (Beta)-HSD2 isozyme. Interestingly, ACTH secreting tumours induce 11β (Beta)-HSD2 expression and may in part explain the re-setting of GC feedback control seen in Cushing's disease [99].

Apparent Mineralocorticoid Excess (AME)

AME is a rare clinical disease that presents in early childhood with hypertension, sodium retention, potassium loss, suppressed renin activity and a metabolic alkalosis [178]. This condition was hallmarked by an increased ratio of urinary cortisol to cortisone metabolites as a result of a lack of conversion of cortisol to cortisone. There was also a low level of circulating of mineralocorticoid despite having evidence of apparent excess with metabolic derangement. Usually fatal in childhood adults with AME were discovered and successfully treated with dexamethasone. Physiological replacement with cortisol caused a return of symptoms and signs [179]. Stewart et al. in 1996 demonstrated that AME was caused by a defect in the 11β (Beta)-HSD2 gene [180] (similar to the effect seen with liquorice ingestion [181]). These and other observations led to the understanding that 11β (Beta)-HSD2 in the kidney protected the mineralocorticoid receptor from glucocorticoid binding. Under normal circumstances 11β (Beta)-HSD2 deactivates cortisol to cortisone and thus protects the MR receptor. In AME, with loss of 11β (Beta)-HSD2 activity unopposed cortisol binds to MR with subsequent clinical mineralocorticoid excess.

The Future of the Dehydrogenase Hypothesis

There is strong evidence that dysregulated 11β (Beta)-HSD1 activity is involved in many pathological processes including obesity and type 2 diabetes. We have also begun to see early clinical trials that demonstrate clinical benefit in 11β (Beta)-HSD1 inhibition. However, whether or not these compounds eventually enter the market with a licence to treat diabetes and metabolic disease remains to be seen. However, they may have utility in other conditions including glaucoma, idiopathic intracranial hypertension and low bone mineral density and clinical trials in these areas are ongoing. In addition, recent work based on observations in a patient with Cushing's disease [182] has suggested that 11β (Beta)-HSD1 may have a role in regulating the phenotype of circulating active GC excess [183]. This not only raises the possibility for the use of 11β (Beta)-HSD1 inhibitors in the treatment of Cushing's syndrome, but also that basal activity may predict the susceptibility to the adverse effects of exogenous GCs and that 11β (Beta)-HSD1 inhibitors could ameliorate the adverse effects, without compromise to the desired actions, of therapeutically indicated GCs.

11β (Beta)-HSD2 has an established role in the regulation of blood pressure and this is highlighted in patients with AME. However, evidence points to an additional role in placental development and function that may have implications for neonatal growth, either directly or through programming. Inhibiting 11β (Beta)-HSD2 action has been shown to stop colorectal adenocarcinoma spread and development and this warrants further investigation [173]. Importantly though, whilst much attention in recent years has focussed on 11β (Beta)-HSD1 activity and therapeutic

inhibition, we must not forget that these two enzymes are tightly associated not least of all because the activity of 11β (Beta)-HSD1 is entirely dependent upon substrate availability (cortisone) that is generated by 11β (Beta)-HSD2. It is entirely plausible that cortisone availability may represent a rate-limiting step regulating 11β (Beta)-HSD1 activity through substrate availability and this needs to be further explored [184].

Inhibition of 11β (Beta)-HSD1 and specifically within tissues is a promising target as a potential disease prevention/modifying pathway. There is strong evidence to date that dysregulated 11β (Beta)-HSD1 activity is involved in many disease states including obesity and diabetes among many. We have also begun to see early human clinical trials that demonstrate clinical benefit with 11β (Beta)-HSD1 inhibition. However, as outlined above both the small number, and the short nature of studies to date have not yielded strong robust evidence to use 11β (Beta)-HSD1 inhibitors. Limited benefits and possible side effects including HPA activation will likely impede and slow the process of these inhibitor compounds from entering phase 3 trials and into clinical use.

One area of possible clinical use, which has not been looked at yet, is to help antagonise the effects of excess glucocorticoid side effects. Published data demonstrate a key role of 11β (Beta)-HSD1 in contributing to GC side effects in Cushing's [182] and in bone metabolism [184]. 11β (Beta)-HSD1 global knock out mice treated with excess GC are protected against GC side effects when compared to wild type controls [183]. This suggests that in conditions with excess circulating GC's, it is the re-activation of cortisone to cortisol within tissues by 11β (Beta)-HSD1, rather than simple cortisol delivery to tissue from the circulation that is the crucial step determining Cushingoid side effects. Data on the role of 11β (Beta)-HSD1 activity in humans with excess GC's is lacking. GC's are widely prescribed with estimates of 1–2 % [185] of the population taking prescribed steroids for various inflammatory conditions. Despite their efficacy, up to 70 % of patients experience an adverse systemic side-effect profile [186]. Inhibiting 11β (Beta)-HSD1 activity may play a beneficial role in preventing glucocorticoid side effects therefore making 11β (Beta)-HSD1 an exciting therapeutic target for patients with Cushing's syndrome.

Lastly, as mentioned previously there is evidence in the literature that 11β (Beta)-HSD1 activity increases with age and is associated with tissue damage and dysfunction. Therefore using tissue specific inhibitors or 11β (Beta)-HSD1 may be a target in conditions such as sarcopaenia and osteoporosis.

Conclusions

Tissue-specific GC metabolism is under the control of the 11β (Beta)-HSD dehydrogenase/reductase enzymes. 11β (Beta)-HSD2 exists to primarily protect mineralocorticoid receptor from excess cortisol exposure in tissues such as kidney. 11β (Beta)-HSD1 exists in many tissues and amplifies tissue exposure to cortisol by

activating cortisol from inert cortisone. Both isoforms have a potent ability to manipulate clinical phenotype entirely independent of circulating GC levels. The complexity of this system and the intricate and finely tuned control that is able to exert at a tissue-specific level to govern ligand access to corticosteroid receptors has highlighted a fundamental shift in our approach. It adds weight to the argument that simple measurement of circulating steroid hormone levels provides an over-simplistic and perhaps misleading view of GC action.

References

1. Munck A, Náray-Fejes-Tóth A. The ups and downs of glucocorticoid physiology. Permissive and suppressive effects revisited. Mol Cell Endocrinol. 1992;90(1):C1–4. http://www.ncbi.nlm.nih.gov/pubmed/1301388. Accessed 31 Dec 2013.
2. Anagnostis P, Katsiki N, Adamidou F, et al. 11beta-Hydroxysteroid dehydrogenase type 1 inhibitors: novel agents for the treatment of metabolic syndrome and obesity-related disorders? Metabolism. 2013;62(1):21–33. doi:10.1016/j.metabol.2012.05.002.
3. Bujalska IL, Kumar SSP. Does central obesity reflect "Cushing's disease of the omentum"? Lancet. 1997;349(9060):1210–3.
4. Tomlinson JW, Sherlock M, Hughes B, et al. Inhibition of 11beta-hydroxysteroid dehydrogenase type 1 activity in vivo limits glucocorticoid exposure to human adipose tissue and decreases lipolysis. J Clin Endocrinol Metab. 2007;92(3):857–64. doi:10.1210/jc.2006-2325.
5. Tomlinson JW, Moore JS, Clark PMS, Holder G, Shakespeare L, Stewart PM. Weight loss increases 11beta-hydroxysteroid dehydrogenase type 1 expression in human adipose tissue. J Clin Endocrinol Metab. 2004;89(6):2711–6. doi:10.1210/jc.2003-031376.
6. Chapman K, Holmes M, Seckl J. 11β-Hydroxysteroid dehydrogenases: intracellular gatekeepers of tissue glucocorticoid action. Physiol Rev. 2013;93(3):1139–206. doi:10.1152/physrev.00020.2012.
7. Tomlinson JW, Walker EA, Bujalska IJ, et al. 11Beta-hydroxysteroid dehydrogenase type 1: a tissue-specific regulator of glucocorticoid response. Endocr Rev. 2004;25(5):831–66. doi:10.1210/er.2003-0031.
8. Feig PU, Shah S, Hermanowski-Vosatka A, et al. Effects of an 11β-hydroxysteroid dehydrogenase type 1 inhibitor, MK-0916, in patients with type 2 diabetes mellitus and metabolic syndrome. Diabetes Obes Metab. 2011;13(6):498–504. doi:10.1111/j.1463-1326.2011.01375.x.
9. Edwards CR, Stewart PM, Burt D, et al. Localisation of 11 beta-hydroxysteroid dehydrogenase—tissue specific protector of the mineralocorticoid receptor. Lancet. 1988;2(8618):986–9. http://www.ncbi.nlm.nih.gov/pubmed/2902493. Accessed 23 Feb 2014.
10. Esteban NV, Loughlin T, Yergey AL, et al. Daily cortisol production rate in man determined by stable isotope dilution/mass spectrometry. J Clin Endocrinol Metab. 1991;72(1):39–45. doi:10.1210/jcem-72-1-39.
11. Keenan DM, Roelfsema F, Veldhuis JD. Endogenous ACTH concentration-dependent drive of pulsatile cortisol secretion in the human. Am J Physiol Endocrinol Metab. 2004;287(4):E652–61. doi:10.1152/ajpendo.00167.2004.
12. Siiteri PK, Murai JT, Hammond GL, Nisker JA, Raymoure WJ, Kuhn RW. The serum transport of steroid hormones. Recent Prog Horm Res. 1982;38:457–510. http://www.ncbi.nlm.nih.gov/pubmed/6750727. Accessed 30 Dec 2013.
13. Dorin RI, Qiao Z, Qualls CR, Urban FK. Estimation of maximal cortisol secretion rate in healthy humans. J Clin Endocrinol Metab. 2012;97(4):1285–93. doi:10.1210/jc.2011-2227.
14. Toothaker RD, Welling PG. Effect of dose size on the pharmacokinetics of intravenous hydrocortisone during endogenous hydrocortisone suppression. J Pharmacokinet Biopharm. 1982;10(2):147–56. http://www.ncbi.nlm.nih.gov/pubmed/7120045. Accessed 9 Feb 2014.

15. Meulenberg PM, Hofman JA. Differences between concentrations of salivary cortisol and cortisone and of free cortisol and cortisone in plasma during pregnancy and postpartum. Clin Chem. 1990;36(1):70–5. http://www.ncbi.nlm.nih.gov/pubmed/2297937. Accessed 7 Mar 2014.
16. Kendall EC. Cortisone: memoirs of a hormone hunter. New York: Charles Scribner's Sons; 1971.
17. Hench PS, Kendall EC. The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone; compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis. Proc Staff Meet Mayo Clin. 1949;24(8):181–97. http://www.ncbi.nlm.nih.gov/pubmed/18118071.
18. Burton RB, Keutmann EH, Waterhouse C, Schuler EA. The conversion of cortisone acetate to other alphaketolic steroids. J Clin Endocrinol Metab. 1953;13(1):48–63. doi:10.1210/jcem-13-1-48.
19. Amelung D, Hubener HJ, Roka L, Meyerheim G. Conversion of cortisone to compound F. J Clin Endocrinol Metab. 1953;13(9):1125–6. doi:10.1210/jcem-13-9-1125.
20. Kavanagh KL, Jörnvall H, Persson B, Oppermann U. Medium- and short-chain dehydrogenase/reductase gene and protein families: the SDR superfamily: functional and structural diversity within a family of metabolic and regulatory enzymes. Cell Mol Life Sci. 2008;65(24):3895–906. doi:10.1007/s00018-008-8588-y.
21. Agarwal AK, Monder C, Eckstein B, White PC. Cloning and expression of rat cDNA encoding corticosteroid 11 beta-dehydrogenase. J Biol Chem. 1989;264(32):18939–43. http://www.ncbi.nlm.nih.gov/pubmed/2808402.
22. Lakshmi V, Monder C. Purification and characterization of the corticosteroid 11 beta-dehydrogenase component of the rat liver 11 beta-hydroxysteroid dehydrogenase complex. Endocrinology. 1988;123(5):2390–8. doi:10.1210/endo-123-5-2390.
23. Tannin GM, Agarwal AK, Monder C, New MI, White PC. The human gene for 11 beta-hydroxysteroid dehydrogenase. Structure, tissue distribution, and chromosomal localization. J Biol Chem. 1991;266(25):16653–8.
24. Nobel CSI, Dunås F, Abrahmsén LB. Purification of full-length recombinant human and rat type 1 11beta-hydroxysteroid dehydrogenases with retained oxidoreductase activities. Protein Expr Purif. 2002;26(3):349–56. http://www.ncbi.nlm.nih.gov/pubmed/12460758. Accessed 5 Jan 2014.
25. Maser E, Völker B, Friebertshäuser J. 11 Beta-hydroxysteroid dehydrogenase type 1 from human liver: dimerization and enzyme cooperativity support its postulated role as glucocorticoid reductase. Biochemistry. 2002;41(7):2459–65. http://www.ncbi.nlm.nih.gov/pubmed/11841241. Accessed 31 Dec 2013.
26. Odermatt A. The N-terminal anchor sequences of 11beta-hydroxysteroid dehydrogenases determine their orientation in the endoplasmic reticulum membrane. J Biol Chem. 1999;274(40):28762–70. doi:10.1074/jbc.274.40.28762.
27. Bujalska IJ, Draper N, Michailidou Z, et al. Hexose-6-phosphate dehydrogenase confers oxoreductase activity upon 11 beta-hydroxysteroid dehydrogenase type 1. J Mol Endocrinol. 2005;34(3):675–84. doi:10.1677/jme.1.01718.
28. Draper N, Walker EA, Bujalska IJ, et al. Mutations in the genes encoding 11beta-hydroxysteroid dehydrogenase type 1 and hexose-6-phosphate dehydrogenase interact to cause cortisone reductase deficiency. Nat Genet. 2003;34(4):434–9. doi:10.1038/ng1214.
29. Murphy VE, Clifton VL. Alterations in human placental 11beta-hydroxysteroid dehydrogenase type 1 and 2 with gestational age and labour. Placenta. 2003;24(7):739–44. http://www.ncbi.nlm.nih.gov/pubmed/12852864. Accessed 12 Feb 2014.
30. Jinno K, Sakura N, Nomura S, Fujitaka M, Ueda K, Kihara M. Failure of cortisone acetate therapy in 21-hydroxylase deficiency in early infancy. Pediatr Int. 2001;43(5):478–82. http://www.ncbi.nlm.nih.gov/pubmed/11737708. Accessed 22 Jan 2014.
31. Murphy BE. Cortisol production and inactivation by the human lung during gestation and infancy. J Clin Endocrinol Metab. 1978;47(2):243–8. doi:10.1210/jcem-47-2-243.
32. Abramovitz M, Branchaud CL, Murphy BE. Cortisol-cortisone interconversion in human fetal lung: contrasting results using explant and monolayer cultures suggest that 11

beta-hydroxysteroid dehydrogenase (EC 1.1.1.146) comprises two enzymes. J Clin Endocrinol Metab. 1982;54(3):563–8. doi:10.1210/jcem-54-3-563.
33. Dimitriou T, Maser-Gluth C, Remer T. Adrenocortical activity in healthy children is associated with fat mass. Am J Clin Nutr. 2003;77(3):731–6. http://www.ncbi.nlm.nih.gov/pubmed/12600869.
34. Toogood AA, Taylor NF, Shalet SM, Monson JP. Sexual dimorphism of cortisol metabolism is maintained in elderly subjects and is not oestrogen dependent. Clin Endocrinol (Oxf). 2000;52(1):61–6. http://www.ncbi.nlm.nih.gov/pubmed/10651754. Accessed 22 Jan 2014.
35. Vierhapper H, Heinze G, Nowotny P. Sex-specific difference in the interconversion of cortisol and cortisone in men and women. Obesity (Silver Spring). 2007;15(4):820–4. doi:10.1038/oby.2007.592.
36. Finken MJ, Andrews RC, Andrew R, Walker BR. Cortisol metabolism in healthy young adults: sexual dimorphism in activities of A-ring reductases, but not 11beta-hydroxysteroid dehydrogenases. J Clin Endocrinol Metab. 1999;84(9):3316–21. doi:10.1210/jcem.84.9.6009.
37. Gathercole LL, Lavery GG, Morgan SA, et al. 11β-hydroxysteroid dehydrogenase 1: translational and therapeutic aspects. Endocr Rev. 2013;34(4):525–55. doi:10.1210/er.2012-1050.
38. Nixon M, Wake DJ, Livingstone DE, et al. Salicylate downregulates 11β-HSD1 expression in adipose tissue in obese mice and in humans, mediating insulin sensitization. Diabetes. 2012;61(4):790–6. doi:10.2337/db11-0931.
39. Paulsen SK, Pedersen SB, Fisker S, Richelsen B. 11Beta-HSD type 1 expression in human adipose tissue: impact of gender, obesity, and fat localization. Obesity (Silver Spring). 2007;15(8):1954–60. doi:10.1038/oby.2007.233.
40. Gomez-Sanchez EP, Ganjam V, Chen YJ, et al. Regulation of 11 beta-hydroxysteroid dehydrogenase enzymes in the rat kidney by estradiol. Am J Physiol Endocrinol Metab. 2003;285(2):E272–9. doi:10.1152/ajpendo.00409.2002.
41. Quirk SJ, Slattery JA, Funder JW. Epithelial and adipose cells isolated from mammary glands of pregnant and lactating rats differ in 11 beta-hydroxysteroid dehydrogenase activity. J Steroid Biochem Mol Biol. 1990;37(4):529–34. http://www.ncbi.nlm.nih.gov/pubmed/2278836. Accessed 31 Dec 2013.
42. Goedecke JH, Wake DJ, Levitt NS, et al. Glucocorticoid metabolism within superficial subcutaneous rather than visceral adipose tissue is associated with features of the metabolic syndrome in South African women. Clin Endocrinol (Oxf). 2006;65(1):81–7. doi:10.1111/j.1365-2265.2006.02552.x.
43. Veilleux A, Laberge PY, Morency J, Noël S, Luu-The V, Tchernof A. Expression of genes related to glucocorticoid action in human subcutaneous and omental adipose tissue. J Steroid Biochem Mol Biol. 2010;122(1–3):28–34. doi:10.1016/j.jsbmb.2010.02.024.
44. Tomlinson JW, Moore J, Cooper MS, et al. Regulation of expression of 11β-hydroxysteroid dehydrogenase type 1 in adipose tissue: tissue-specific induction by cytokines. Endocrinology. 2001;142(5):1982–9.
45. Friedberg M, Zoumakis E, Hiroi N, Bader T, Chrousos GP, Hochberg Z. Modulation of 11 beta-hydroxysteroid dehydrogenase type 1 in mature human subcutaneous adipocytes by hypothalamic messengers. J Clin Endocrinol Metab. 2003;88(1):385–93. doi:10.1210/jc.2002-020510.
46. Handoko K, Yang K, Strutt B, Khalil W, Killinger D. Insulin attenuates the stimulatory effects of tumor necrosis factor alpha on 11beta-hydroxysteroid dehydrogenase 1 in human adipose stromal cells. J Steroid Biochem Mol Biol. 2000;72(3–4):163–8. http://www.ncbi.nlm.nih.gov/pubmed/10775808. Accessed 31 Dec 2013.
47. Esteves CL, Kelly V, Breton A, et al. Proinflammatory cytokine induction of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) in human adipocytes is mediated by MEK, C/EBPβ, and NF-κB/RelA. J Clin Endocrinol Metab. 2014;99(1):E160–8. doi:10.1210/jc.2013-1708.
48. Bujalska IJ, Walker EA, Hewison M, Stewart PM. A switch in dehydrogenase to reductase activity of 11 beta-hydroxysteroid dehydrogenase type 1 upon differentiation of human omental adipose stromal cells. J Clin Endocrinol Metab. 2002;87(3):1205–10. doi:10.1210/jcem.87.3.8301.

49. Bujalska IJ, Gathercole LL, Tomlinson JW, et al. A novel selective 11beta-hydroxysteroid dehydrogenase type 1 inhibitor prevents human adipogenesis. J Endocrinol. 2008; 197(2):297–307. doi:10.1677/JOE-08-0050.
50. Livingstone DE, Kenyon CJ, Walker BR. Mechanisms of dysregulation of 11 beta-hydroxysteroid dehydrogenase type 1 in obese Zucker rats. J Endocrinol. 2000;167(3):533–9. http://www.ncbi.nlm.nih.gov/pubmed/11115781. Accessed 7 Mar 2014.
51. Livingstone DE, Jones GC, Smith K, et al. Understanding the role of glucocorticoids in obesity: tissue-specific alterations of corticosterone metabolism in obese Zucker rats. Endocrinology. 2000;141(2):560–3. doi:10.1210/endo.141.2.7297.
52. Morton NM, Ramage L, Seckl JR. Down-regulation of adipose 11beta-hydroxysteroid dehydrogenase type 1 by high-fat feeding in mice: a potential adaptive mechanism counteracting metabolic disease. Endocrinology. 2004;145(6):2707–12. doi:10.1210/en.2003-1674.
53. Drake AJ, Livingstone DEW, Andrew R, Seckl JR, Morton NM, Walker BR. Reduced adipose glucocorticoid reactivation and increased hepatic glucocorticoid clearance as an early adaptation to high-fat feeding in Wistar rats. Endocrinology. 2005;146(2):913–9. doi:10.1210/en.2004-1063.
54. Morton NM, Holmes MC, Fiévet C, et al. Improved lipid and lipoprotein profile, hepatic insulin sensitivity, and glucose tolerance in 11beta-hydroxysteroid dehydrogenase type 1 null mice. J Biol Chem. 2001;276(44):41293–300. doi:10.1074/jbc.M103676200.
55. Masuzaki H, Paterson J, Shinyama H, et al. A transgenic model of visceral obesity and the metabolic syndrome. Science. 2001;294(5549):2166–70. doi:10.1126/science.1066285.
56. Rask E. Tissue-specific dysregulation of cortisol metabolism in human obesity. J Clin Endocrinol Metab. 2001;86(3):1418–21. doi:10.1210/jc.86.3.1418.
57. Lindsay RS. Subcutaneous adipose 11-hydroxysteroid dehydrogenase type 1 activity and messenger ribonucleic acid levels are associated with adiposity and insulinemia in Pima Indians and Caucasians. J Clin Endocrinol Metab. 2003;88(6):2738–44. doi:10.1210/jc.2002-030017.
58. Veilleux A, Rhéaume C, Daris M, Luu-The V, Tchernof A. Omental adipose tissue type 1 11 beta-hydroxysteroid dehydrogenase oxoreductase activity, body fat distribution, and metabolic alterations in women. J Clin Endocrinol Metab. 2009;94(9):3550–7. doi:10.1210/jc.2008-2011.
59. Lee JH, Gao Z, Ye J. Regulation of 11β-HSD1 expression during adipose tissue expansion by hypoxia through different activities of NF-κB and HIF-1α. Am J Physiol Endocrinol Metab. 2013;304(10):E1035–41. doi:10.1152/ajpendo.00029.2013.
60. McCormick KL, Wang X, Mick GJ. Evidence that the 11 beta-hydroxysteroid dehydrogenase (11 beta-HSD1) is regulated by pentose pathway flux. Studies in rat adipocytes and microsomes. J Biol Chem. 2006;281(1):341–7. doi:10.1074/jbc.M506026200.
61. Gout J, Tirard J, Thévenon C, Riou J-P, Bégeot M, Naville D. CCAAT/enhancer-binding proteins (C/EBPs) regulate the basal and cAMP-induced transcription of the human 11beta-hydroxysteroid dehydrogenase encoding gene in adipose cells. Biochimie. 2006;88(9):1115–24. doi:10.1016/j.biochi.2006.05.020.
62. Esteves CL, Kelly V, Bégay V, et al. Regulation of adipocyte 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) by CCAAT/enhancer-binding protein (C/EBP) β isoforms LIP and LAP. PLoS One. 2012;7(5):e37953. doi:10.1371/journal.pone.0037953.
63. Amatruda JM, Danahy SA, Chang CL. The effects of glucocorticoids on insulin-stimulated lipogenesis in primary cultures of rat hepatocytes. Biochem J. 1983;212(1):135–41. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1152020&tool=pmcentrez&rendertype=abstract.
64. Dolinsky VW, Douglas DN, Lehner R, Vance DE. Regulation of the enzymes of hepatic microsomal triacylglycerol lipolysis and re-esterification by the glucocorticoid dexamethasone. Biochem J. 2004;378(Pt 3):967–74. doi:10.1042/BJ20031320.
65. Baxter JD, Forsham PH. Tissue effects of glucocorticoids. Am J Med. 1972;53(5):573–89. http://www.ncbi.nlm.nih.gov/pubmed/4342884. Accessed 22 Jan 2014.

66. Paterson JM, Morton NM, Fievet C, et al. Metabolic syndrome without obesity: hepatic overexpression of 11beta-hydroxysteroid dehydrogenase type 1 in transgenic mice. Proc Natl Acad Sci U S A. 2004;101(18):7088–93. doi:10.1073/pnas.0305524101.
67. Ricketts ML, Verhaeg JM, Bujalska I, Howie AJ, Rainey WE, Stewart PM. Immunohistochemical localization of type 1 11beta-hydroxysteroid dehydrogenase in human tissues. J Clin Endocrinol Metab. 1998;83(4):1325–35. doi:10.1210/jcem.83.4.4706.
68. Jamieson PM, Walker BR, Chapman KE, Andrew R, Rossiter S, Seckl JR. 11 beta-hydroxysteroid dehydrogenase type 1 is a predominant 11 beta-reductase in the intact perfused rat liver. J Endocrinol. 2000;165(3):685–92. http://www.ncbi.nlm.nih.gov/pubmed/10828853. Accessed 7 Mar 2014.
69. Candia R, Riquelme A, Baudrand R, et al. Overexpression of 11β-hydroxysteroid dehydrogenase type 1 in visceral adipose tissue and portal hypercortisolism in non-alcoholic fatty liver disease. Liver Int. 2012;32(3):392–9. doi:10.1111/j.1478-3231.2011.02685.x.
70. Baudrand R, Carvajal CA, Riquelme A, et al. Overexpression of 11beta-hydroxysteroid dehydrogenase type 1 in hepatic and visceral adipose tissue is associated with metabolic disorders in morbidly obese patients. Obes Surg. 2010;20(1):77–83. doi:10.1007/s11695-009-9937-0.
71. Konopelska S, Kienitz T, Hughes B, et al. Hepatic 11beta-HSD1 mRNA expression in fatty liver and nonalcoholic steatohepatitis. Clin Endocrinol (Oxf). 2009;70(4):554–60. doi:10.1111/j.1365-2265.2008.03358.x.
72. Torrecilla E, Fernández-Vázquez G, Vicent D, et al. Liver upregulation of genes involved in cortisol production and action is associated with metabolic syndrome in morbidly obese patients. Obes Surg. 2012;22(3):478–86. doi:10.1007/s11695-011-0524-9.
73. Valsamakis G, Anwar A, Tomlinson JW, et al. 11Beta-hydroxysteroid dehydrogenase type 1 activity in lean and obese males with type 2 diabetes mellitus. J Clin Endocrinol Metab. 2004;89(9):4755–61. doi:10.1210/jc.2003-032240.
74. Ahmed A, Rabbitt E, Brady T, et al. A switch in hepatic cortisol metabolism across the spectrum of non alcoholic fatty liver disease. PLoS One. 2012;7(2):e29531. doi:10.1371/journal.pone.0029531.
75. Whorwood CB, Donovan SJ, Flanagan D, Phillips DIW, Byrne CD. Increased glucocorticoid receptor expression in human skeletal muscle cells may contribute to the pathogenesis of the metabolic syndrome. Diabetes. 2002;51(4):1066–75. http://www.ncbi.nlm.nih.gov/pubmed/11916927.
76. Whorwood CB, Donovan SJ, Wood PJ, Phillips DI. Regulation of glucocorticoid receptor alpha and beta isoforms and type I 11β-hydroxysteroid dehydrogenase expression in human skeletal muscle cells: a key role in the pathogenesis of insulin resistance? J Clin Endocrinol Metab. 2001;86(5):2296–308.
77. Morgan SA, Sherlock M, Gathercole LL, et al. 11beta-hydroxysteroid dehydrogenase type 1 regulates glucocorticoid-induced insulin resistance in skeletal muscle. Diabetes. 2009;58(11):2506–15. doi:10.2337/db09-0525.
78. Abdallah BM, Beck-Nielsen H, Gaster M. Increased expression of 11beta-hydroxysteroid dehydrogenase type 1 in type 2 diabetic myotubes. Eur J Clin Invest. 2005;35(10):627–34. doi:10.1111/j.1365-2362.2005.01552.x.
79. Zhang M, Lv X-Y, Li J, Xu Z-G, Chen L. Alteration of 11beta-hydroxysteroid dehydrogenase type 1 in skeletal muscle in a rat model of type 2 diabetes. Mol Cell Biochem. 2009;324(1–2):147–55. doi:10.1007/s11010-008-9993-0.
80. Kilgour AHM, Gallagher IJ, Maclullich AMJ, et al. Increased skeletal muscle 11βHSD1 mRNA is associated with lower muscle strength in ageing. PLoS One. 2013;8(12):e84057. doi:10.1371/journal.pone.0084057.
81. Vukelic S, Stojadinovic O, Pastar I, et al. Cortisol synthesis in epidermis is induced by IL-1 and tissue injury. J Biol Chem. 2011;286(12):10265–75. doi:10.1074/jbc.M110.188268.
82. Tiganescu A, Walker EA, Hardy RS, Mayes AE, Stewart PM. Localization, age- and site-dependent expression, and regulation of 11β-hydroxysteroid dehydrogenase type 1 in skin. J Invest Dermatol. 2011;131(1):30–6. doi:10.1038/jid.2010.257.

83. Fisher GJ, Varani J, Voorhees JJ. Looking older: fibroblast collapse and therapeutic implications. Arch Dermatol. 2010;144(5):666–72. doi:10.1001/archderm.144.5.666.Looking.
84. Slominski A, Zbytek B, Nikolakis G, et al. Steroidogenesis in the skin: implications for local immune functions. J Steroid Biochem Mol Biol. 2013;137:107–23. doi:10.1016/j.jsbmb.2013.02.006.
85. Terao M, Murota H, Kimura A, et al. 11β-Hydroxysteroid dehydrogenase-1 is a novel regulator of skin homeostasis and a candidate target for promoting tissue repair. PLoS One. 2011;6(9):e25039. doi:10.1371/journal.pone.0025039.
86. Cirillo N, Prime SS. Keratinocytes synthesize and activate cortisol. J Cell Biochem. 2011;112(6):1499–505. doi:10.1002/jcb.23081.
87. Napolitano A, Voice MW, Edwards CR, Seckl JR, Chapman KE. 11Beta-hydroxysteroid dehydrogenase 1 in adipocytes: expression is differentiation-dependent and hormonally regulated. J Steroid Biochem Mol Biol. 1998;64(5–6):251–60. http://www.ncbi.nlm.nih.gov/pubmed/9618026. Accessed 3 Feb 2014.
88. Tiganescu A, Hupe M, Uchida Y, Mauro T, Elias PM, Holleran W. Increased glucocorticoid activation during mouse skin wound healing. J Endocrinol. 2014;221(1):51–61. doi:10.1530/JOE-13-0420.
89. Tiganescu A, Tahrani AA, Morgan SA, et al. 11β-Hydroxysteroid dehydrogenase blockade prevents age-induced skin structure and function defects. J Clin Invest. 2013;123(7):3051–60. doi:10.1172/JCI64162.
90. Brem AS, Bina RB, King TC, Morris DJ. Localization of 2 11beta-OH steroid dehydrogenase isoforms in aortic endothelial cells. Hypertension. 1998;31(1 Pt 2):459–62. http://www.ncbi.nlm.nih.gov/pubmed/9453345. Accessed 14 Feb 2014.
91. Walker BR, Yau JL, Brett LP, et al. 11 beta-hydroxysteroid dehydrogenase in vascular smooth muscle and heart: implications for cardiovascular responses to glucocorticoids. Endocrinology. 1991;129(6):3305–12. doi:10.1210/endo-129-6-3305.
92. Atalar F, Gormez S, Caynak B, et al. The role of mediastinal adipose tissue 11β-hydroxysteroid dehydrogenase type 1 and glucocorticoid expression in the development of coronary atherosclerosis in obese patients with ischemic heart disease. Cardiovasc Diabetol. 2012;11:115. doi:10.1186/1475-2840-11-115.
93. Atalar F, Vural B, Ciftci C, et al. 11β-hydroxysteroid dehydrogenase type 1 gene expression is increased in ascending aorta tissue of metabolic syndrome patients with coronary artery disease. Genet Mol Res. 2012;11(3):3122–32. doi:10.4238/2012.August.31.10.
94. Hermanowski-Vosatka A, Balkovec JM, Cheng K, et al. 11beta-HSD1 inhibition ameliorates metabolic syndrome and prevents progression of atherosclerosis in mice. J Exp Med. 2005;202(4):517–27. doi:10.1084/jem.20050119.
95. Nuotio-Antar AM, Hachey DL, Hasty AH. Carbenoxolone treatment attenuates symptoms of metabolic syndrome and atherogenesis in obese, hyperlipidemic mice. Am J Physiol Endocrinol Metab. 2007;293(6):E1517–28. doi:10.1152/ajpendo.00522.2007.
96. Small GR, Hadoke PWF, Sharif I, et al. Preventing local regeneration of glucocorticoids by 11beta-hydroxysteroid dehydrogenase type 1 enhances angiogenesis. Proc Natl Acad Sci U S A. 2005;102(34):12165–70. doi:10.1073/pnas.0500641102.
97. Brown ES. Effects of glucocorticoids on mood, memory, and the hippocampus. Treatment and preventive therapy. Ann N Y Acad Sci. 2009;1179:41–55. doi:10.1111/j.1749-6632.2009.04981.x.
98. Swaab DF, Bao A-M, Lucassen PJ. The stress system in the human brain in depression and neurodegeneration. Ageing Res Rev. 2005;4(2):141–94. doi:10.1016/j.arr.2005.03.003.
99. Korbonits M, Bujalska I, Shimojo M, et al. Expression of 11 beta-hydroxysteroid dehydrogenase isoenzymes in the human pituitary: induction of the type 2 enzyme in corticotropinomas and other pituitary tumors. J Clin Endocrinol Metab. 2001;86(6):2728–33. doi:10.1210/jcem.86.6.7563.
100. Moisan MP, Seckl JR, Edwards CR. 11 beta-hydroxysteroid dehydrogenase bioactivity and messenger RNA expression in rat forebrain: localization in hypothalamus, hippocampus, and cortex. Endocrinology. 1990;127(3):1450–5. doi:10.1210/endo-127-3-1450.

101. Gomez-Sanchez EP, Romero DG, de Rodriguez AF, Warden MP, Krozowski Z, Gomez-Sanchez CE. Hexose-6-phosphate dehydrogenase and 11beta-hydroxysteroid dehydrogenase-1 tissue distribution in the rat. Endocrinology. 2008;149(2):525–33. doi:10.1210/en.2007-0328.
102. Lakshmi V, Sakai RR, McEwen BS, Monder C. Regional distribution of 11 beta-hydroxysteroid dehydrogenase in rat brain. Endocrinology. 1991;128(4):1741–8. doi:10.1210/endo-128-4-1741.
103. Rajan V, Edwards RW, Seckl JR. 11 beta-hydroxysteroid dehydrogenase in cultured cells reactivates inert 11-dehydrocorticosterone, potentiating neurotoxicity hippocampal. J Neurosci. 1996;76(1):65–70.
104. Wyrwoll CS, Holmes MC, Seckl JR. 11β-hydroxysteroid dehydrogenases and the brain: from zero to hero, a decade of progress. Front Neuroendocrinol. 2011;32(3):265–86. doi:10.1016/j.yfrne.2010.12.001.
105. Tomlinson JW, Durrani OM, Bujalska IJ, et al. The role of 11beta-hydroxysteroid dehydrogenase 1 in adipogenesis in thyroid-associated ophthalmopathy. J Clin Endocrinol Metab. 2010;95(1):398–406. doi:10.1210/jc.2009-0873.
106. Sandeep TC, Yau JLW, MacLullich AMJ, et al. 11Beta-hydroxysteroid dehydrogenase inhibition improves cognitive function in healthy elderly men and type 2 diabetics. Proc Natl Acad Sci U S A. 2004;101(17):6734–9. doi:10.1073/pnas.0306996101.
107. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids—new mechanisms for old drugs. N Engl J Med. 2005;353(16):1711–23. doi:10.1056/NEJMra050541.
108. Chapman KE, Coutinho AE, Gray M, Gilmour JS, Savill JS, Seckl JR. The role and regulation of 11beta-hydroxysteroid dehydrogenase type 1 in the inflammatory response. Mol Cell Endocrinol. 2009;301(1-2):123–31. doi:10.1016/j.mce.2008.09.031.
109. Coutinho AE, Brown JK, Yang F, et al. Mast cells express 11β-hydroxysteroid dehydrogenase type 1: a role in restraining mast cell degranulation. PLoS One. 2013;8(1):e54640. doi:10.1371/journal.pone.0054640.
110. Thieringer R, Le Grand CB, Carbin L, et al. 11 Beta-hydroxysteroid dehydrogenase type 1 is induced in human monocytes upon differentiation to macrophages. J Immunol. 2001;167(1):30–5. http://www.ncbi.nlm.nih.gov/pubmed/11418628.
111. Zhang TY, Ding X, Daynes RA, Alerts E. Regulation of glucocorticoid activities 1. J Immunol. 2005;174(2):879–89.
112. Freeman L, Hewison M, Hughes SV, et al. Expression of 11β-hydroxysteroid dehydrogenase type 1 permits regulation of glucocorticoid bioavailability by human dendritic cells. Blood. 2005;106(6):2042–9. doi:10.1182/blood-2005-01-0186.
113. Gilmour JS, Coutinho AE, Cailhier J, et al. Local amplification of glucocorticoids by 11β-hydroxysteroid dehydrogenase type 1 promotes macrophage phagocytosis of apoptotic leukocytes. J Immunol. 2006;176(12):7605–11.
114. Zhang TY, Daynes RA. Macrophages from 11beta-hydroxysteroid dehydrogenase type 1-deficient mice exhibit an increased sensitivity to lipopolysaccharide stimulation due to TGF-beta-mediated up-regulation of SHIP1 expression. J Immunol. 2007;179(9):6325–35.
115. Coutinho AE, Gray M, Brownstein DG, et al. 11β-Hydroxysteroid dehydrogenase type 1, but not type 2, deficiency worsens acute inflammation and experimental arthritis in mice. Endocrinology. 2012;153(1):234–40. doi:10.1210/en.2011-1398.
116. Zbánková S, Bryndová J, Leden P, Kment M, Svec A, Pácha J. 11beta-hydroxysteroid dehydrogenase 1 and 2 expression in colon from patients with ulcerative colitis. J Gastroenterol Hepatol. 2007;22(7):1019–23. doi:10.1111/j.1440-1746.2006.04529.x.
117. Stegk JP, Ebert B, Martin H-J, Maser E. Expression profiles of human 11beta-hydroxysteroid dehydrogenases type 1 and type 2 in inflammatory bowel diseases. Mol Cell Endocrinol. 2009;301(1–2):104–8. doi:10.1016/j.mce.2008.10.030.
118. Cooper MS, Kriel H, Sayers A, et al. Can 11β-hydroxysteroid dehydrogenase activity predict the sensitivity of bone to therapeutic glucocorticoids in inflammatory bowel disease? Calcif Tissue Int. 2011;89(3):246–51. doi:10.1007/s00223-011-9512-2.

119. Ergang P, Vytáčková K, Svec J, Bryndová J, Mikšík I, Pácha J. Upregulation of 11β-hydroxysteroid dehydrogenase 1 in lymphoid organs during inflammation in the rat. J Steroid Biochem Mol Biol. 2011;126(1–2):19–25. doi:10.1016/j.jsbmb.2011.04.002.
120. Cooper MS, Walker EA, Bland R, Fraser WD, Hewison M, Stewart PM. Expression and functional consequences of 11beta-hydroxysteroid dehydrogenase activity in human bone. Bone. 2000;27(3):375–81. http://www.ncbi.nlm.nih.gov/pubmed/10962348. Accessed 14 Feb 2014.
121. Bellows CG, Ciaccia A, Heersche JN. Osteoprogenitor cells in cell populations derived from mouse and rat calvaria differ in their response to corticosterone, cortisol, and cortisone. Bone. 1998;23(2):119–25. http://www.ncbi.nlm.nih.gov/pubmed/9701470. Accessed 14 Feb 2014.
122. Hardy R, Rabbitt EH, Filer A, et al. Local and systemic glucocorticoid metabolism in inflammatory arthritis. Ann Rheum Dis. 2008;67(9):1204–10. doi:10.1136/ard.2008.090662.
123. Schmidt M, Weidler C, Naumann H, Anders S, Schölmerich J, Straub RH. Reduced capacity for the reactivation of glucocorticoids in rheumatoid arthritis synovial cells: possible role of the sympathetic nervous system? Arthritis Rheum. 2005;52(6):1711–20. doi:10.1002/art.21091.
124. Ergang P, Leden P, Vagnerová K, et al. Local metabolism of glucocorticoids and its role in rat adjuvant arthritis. Mol Cell Endocrinol. 2010;323(2):155–60. doi:10.1016/j.mce.2010.03.003.
125. Lavery GG, Walker EA, Tiganescu A, et al. Steroid biomarkers and genetic studies reveal inactivating mutations in hexose-6-phosphate dehydrogenase in patients with cortisone reductase deficiency. J Clin Endocrinol Metab. 2008;93(10):3827–32. doi:10.1210/jc.2008-0743.
126. Morgan SA, Tomlinson JW. 11beta-hydroxysteroid dehydrogenase type 1 inhibitors for the treatment of type 2 diabetes. Expert Opin Investig Drugs. 2010;19(9):1067–76. doi:10.1517/13543784.2010.504713.
127. Monder C, Lakshmi V. Evidence for kinetically distinct forms of corticosteroid 11 beta-dehydrogenase in rat liver microsomes. J Steroid Biochem. 1989;32(1A):77–83. http://www.ncbi.nlm.nih.gov/pubmed/2913404. Accessed 23 Jan 2014.
128. Schweizer RAS, Atanasov AG, Frey BM, Odermatt A. A rapid screening assay for inhibitors of 11beta-hydroxysteroid dehydrogenases (11beta-HSD): flavanone selectively inhibits 11beta-HSD1 reductase activity. Mol Cell Endocrinol. 2003;212(1–2):41–9. http://www.ncbi.nlm.nih.gov/pubmed/14654249. Accessed 23 Jan 2014.
129. Diederich S, Grossmann C, Hanke B, et al. In the search for specific inhibitors of human 11beta-hydroxysteroid-dehydrogenases (11beta-HSDs): chenodeoxycholic acid selectively inhibits 11beta-HSD-I. Eur J Endocrinol. 2000;142(2):200–7. http://www.ncbi.nlm.nih.gov/pubmed/10664531.
130. Latif SA, Pardo HA, Hardy MP, Morris DJ. Endogenous selective inhibitors of 11beta-hydroxysteroid dehydrogenase isoforms 1 and 2 of adrenal origin. Mol Cell Endocrinol. 2005;243(1–2):43–50. doi:10.1016/j.mce.2005.08.006.
131. Atanasov AG, Dzyakanchuk AA, Schweizer RAS, Nashev LG, Maurer EM, Odermatt A. Coffee inhibits the reactivation of glucocorticoids by 11beta-hydroxysteroid dehydrogenase type 1: a glucocorticoid connection in the anti-diabetic action of coffee? FEBS Lett. 2006;580(17):4081–5. doi:10.1016/j.febslet.2006.06.046.
132. Andrews RC, Rooyackers O, Walker BR. Effects of the 11 beta-hydroxysteroid dehydrogenase inhibitor carbenoxolone on insulin sensitivity in men with type 2 diabetes. J Clin Endocrinol Metab. 2003;88(1):285–91. doi:10.1210/jc.2002-021194.
133. Reuters T. The changing role of chemistry in drug discovery. 2011. http://thomsonreuters.com/content/dam/openweb/documents/pdf/pharma-life-sciences/report/international-year-of-chemistry-report-drug-discovery.pdf.
134. Boyle CD, Kowalski TJ. 11beta-hydroxysteroid dehydrogenase type 1 inhibitors: a review of recent patents. Expert Opin Ther Pat. 2009;19(6):801–25. doi: 10.1517/13543770902967658.
135. Rosenstock J, Banarer S, Fonseca VA, et al. The 11-beta-hydroxysteroid dehydrogenase type 1 inhibitor INCB13739 improves hyperglycemia in patients with type 2 diabetes inadequately

controlled by metformin monotherapy. Diabetes Care. 2010;33(7):1516–22. doi:10.2337/dc09-2315.
136. Shah S, Hermanowski-Vosatka A, Gibson K, et al. Efficacy and safety of the selective 11β-HSD-1 inhibitors MK-0736 and MK-0916 in overweight and obese patients with hypertension. J Am Soc Hypertens. 2011;5(3):166–76. doi:10.1016/j.jash.2011.01.009.
137. Brown RW, Chapman KE, Edwards CR, Seckl JR. Human placental 11 beta-hydroxysteroid dehydrogenase: evidence for and partial purification of a distinct NAD-dependent isoform. Endocrinology. 1993;132(6):2614–21. doi:10.1210/endo.132.6.8504762.
138. Albiston AL, Obeyesekere VR, Smith RE, Krozowski ZS. Cloning and tissue distribution of the human 11 beta-hydroxysteroid dehydrogenase type 2 enzyme. Mol Cell Endocrinol. 1994;105(2):R11–7. http://www.ncbi.nlm.nih.gov/pubmed/7859916. Accessed 5 Feb 2014.
139. Persson B, Kallberg Y, Bray JE, et al. The SDR (short-chain dehydrogenase/reductase and related enzymes) nomenclature initiative. Chem Biol Interact. 2009;178(1–3):94–8. doi:10.1016/j.cbi.2008.10.040.
140. Agarwal AK, Rogerson FM, Mune T, White PC. Gene structure and chromosomal localization of the human HSD11K gene encoding the kidney (type 2) isozyme of 11 beta-hydroxysteroid dehydrogenase. Genomics. 1995;29(1):195–9. doi:10.1006/geno.1995.1231.
141. Brown RW, Chapman KE, Kotelevtsev Y, et al. Cloning and production of antisera to human placental 11β-hydroxysteroid dehydrogenase type 2. Biochem J. 1996;313:1007–17.
142. Stewart PM, Murry BA, Mason JI. Human kidney 11 beta-hydroxysteroid dehydrogenase is a high affinity nicotinamide adenine dinucleotide-dependent enzyme and differs from the cloned type I isoform. J Clin Endocrinol Metab. 1994;79(2):480–4. doi:10.1210/jcem.79.2.8045966.
143. Dave-Sharma S, Wilson RC, Harbison MD, et al. Examination of genotype and phenotype relationships in 14 patients with apparent mineralocorticoid excess. J Clin Endocrinol Metab. 1998;83(7):2244–54. doi:10.1210/jcem.83.7.4986.
144. Wilson RC, Krozowski ZS, Li K, et al. A mutation in the HSD11B2 gene in a family with apparent mineralocorticoid excess. J Clin Endocrinol Metab. 1995;80(7):2263–6. doi:10.1210/jcem.80.7.7608290.
145. Mune T, Rogerson FM, Nikkilä H, Agarwal AK, White PC. Human hypertension caused by mutations in the kidney isozyme of 11 beta-hydroxysteroid dehydrogenase. Nat Genet. 1995;10(4):394–9. doi:10.1038/ng0895-394.
146. Osinski PA. Steroid 11beta-ol dehydrogenase in human placenta. Nature. 1960;187:777. http://www.ncbi.nlm.nih.gov/pubmed/14429221. Accessed 31 Dec 2013.
147. Waffarn F, Davis EP. Effects of antenatal corticosteroids on the hypothalamic-pituitary-adrenocortical axis of the fetus and newborn: experimental findings and clinical considerations. Am J Obstet Gynecol. 2012;207(6):446–54. doi:10.1016/j.ajog.2012.06.012.
148. Wyrwoll CS, Holmes MC. Prenatal excess glucocorticoid exposure and adult affective disorders: a role for serotonergic and catecholamine pathways. Neuroendocrinology. 2012;95(1):47–55. doi:10.1159/000331345.
149. Huang WL, Beazley LD, Quinlivan JA, Evans SF, Newnham JP, Dunlop SA. Effect of corticosteroids on brain growth in fetal sheep. Obstet Gynecol. 1999;94(2):213–8. http://www.ncbi.nlm.nih.gov/pubmed/10432130. Accessed 14 Feb 2014.
150. Seckl JR, Holmes MC. Mechanisms of disease: glucocorticoids, their placental metabolism and fetal "programming" of adult pathophysiology. Nat Clin Pract Endocrinol Metab. 2007;3(6):479–88. doi:10.1038/ncpendmet0515.
151. Alikhani-Koopaei R, Fouladkou F, Frey FJ, Frey BM. Epigenetic regulation of 11 beta-hydroxysteroid dehydrogenase type 2 expression. J Clin Invest. 2004;114(8):1146–57. doi:10.1172/JCI21647.
152. Marsit CJ, Maccani MA, Padbury JF, Lester BM. Placental 11-beta hydroxysteroid dehydrogenase methylation is associated with newborn growth and a measure of neurobehavioral outcome. PLoS One. 2012;7(3):e33794. doi:10.1371/journal.pone.0033794.
153. Baserga M, Kaur R, Hale MA, et al. Fetal growth restriction alters transcription factor binding and epigenetic mechanisms of renal 11β-hydroxysteroid dehydrogenase type 2 in a sex-

specific manner. Am J Physiol Regul Integr Comp Physiol. 2010;299(1):334–42. doi:10.1152/ajpregu.00122.2010.
154. Kostadinova RM, Nawrocki AR, Frey FJ, Frey BM. Tumor necrosis factor alpha and phorbol 12-myristate-13-acetate down-regulate human 11beta-hydroxysteroid dehydrogenase type 2 through p50/p50 NF-kappaB homodimers and Egr-1. FASEB J. 2005;19(6):650–2. doi:10.1096/fj.04-2820fje.
155. Low SC, Assaad SN, Rajan V, Chapman KE, Edwards CR, Seckl JR. Regulation of 11 beta-hydroxysteroid dehydrogenase by sex steroids in vivo: further evidence for the existence of a second dehydrogenase in rat kidney. J Endocrinol. 1993;139(1):27–35. http://www.ncbi.nlm.nih.gov/pubmed/8254291. Accessed 13 Feb 2014.
156. Rubis B, Krozowski Z, Trzeciak WH. Arginine vasopressin stimulates 11beta-hydroxysteroid dehydrogenase type 2 expression in the mineralocorticosteroid target cells. Mol Cell Endocrinol. 2006;256(1–2):17–22. doi:10.1016/j.mce.2006.04.032.
157. Clarke KA, Ward JW, Forhead AJ, Giussani DA, Fowden AL. Regulation of 11 beta-hydroxysteroid dehydrogenase type 2 activity in ovine placenta by fetal cortisol. J Endocrinol. 2002;172(3):527–34. http://www.ncbi.nlm.nih.gov/pubmed/11874701. Accessed 13 Feb 2014.
158. Suzuki S, Koyama K, Darnel A, et al. Dexamethasone upregulates 11beta-hydroxysteroid dehydrogenase type 2 in BEAS-2B cells. Am J Respir Crit Care Med. 2003;167(9):1244–9. doi:10.1164/rccm.200210-1139OC.
159. Heiniger CD, Kostadinova RM, Rochat MK, et al. Hypoxia causes down-regulation of 11 beta-hydroxysteroid dehydrogenase type 2 by induction of Egr-1. FASEB J. 2003;17(8):917–9. doi:10.1096/fj.02-0582fje.
160. Fukushima K, Funayama Y, Yonezawa H, et al. Aldosterone enhances 11beta-hydroxysteroid dehydrogenase type 2 expression in colonic epithelial cells in vivo. Scand J Gastroenterol. 2005;40(7):850–7. doi:10.1080/00365520510015700.
161. Geerling JC, Loewy AD. Aldosterone in the brain. Am J Physiol Renal Physiol. 2009;297(3):F559–76. doi:10.1152/ajprenal.90399.2008.
162. Holmes MC, Sangra M, French KL, et al. 11beta-hydroxysteroid dehydrogenase type 2 protects the neonatal cerebellum from deleterious effects of glucocorticoids. Neuroscience. 2006;137(3):865–73. doi:10.1016/j.neuroscience.2005.09.037.
163. Noguchi KK, Lau K, Smith DJ, Swiney BS, Farber NB. Glucocorticoid receptor stimulation and the regulation of neonatal cerebellar neural progenitor cell apoptosis. Neurobiol Dis. 2011;43(2):356–63. doi:10.1016/j.nbd.2011.04.004.
164. Roland BL, Li KX, Funder JW. Hybridization histochemical localization of 11 beta-hydroxysteroid dehydrogenase type 2 in rat brain. Endocrinology. 1995;136(10):4697–700. doi:10.1210/endo.136.10.7664691.
165. Christy C, Hadoke PWF, Paterson JM, Mullins JJ, Seckl JR, Walker BR. 11beta-hydroxysteroid dehydrogenase type 2 in mouse aorta: localization and influence on response to glucocorticoids. Hypertension. 2003;42(4):580–7. doi:10.1161/01.HYP.0000088855.06598.5B.
166. Deuchar GA, McLean D, Hadoke PWF, et al. 11β-hydroxysteroid dehydrogenase type 2 deficiency accelerates atherogenesis and causes proinflammatory changes in the endothelium in apoe-/- mice. Endocrinology. 2011;152(1):236–46. doi:10.1210/en.2010-0925.
167. Leckie C, Chapman KE, Edwards CR, Seckl JR. LLC-PK1 cells model 11 beta-hydroxysteroid dehydrogenase type 2 regulation of glucocorticoid access to renal mineralocorticoid receptors. Endocrinology. 1995;136(12):5561–9. doi:10.1210/endo.136.12.7588309.
168. Henschkowski J, Stuck AE, Frey BM, et al. Age-dependent decrease in 11beta-hydroxysteroid dehydrogenase type 2 (11beta-HSD2) activity in hypertensive patients. Am J Hypertens. 2008;21(6):644–9. doi:10.1038/ajh.2008.152.
169. Ferrari P. The role of 11β-hydroxysteroid dehydrogenase type 2 in human hypertension. Biochim Biophys Acta. 2010;1802(12):1178–87. doi:10.1016/j.bbadis.2009.10.017.
170. Mongia A, Vecker R, George M, et al. Role of 11βHSD type 2 enzyme activity in essential hypertension and children with chronic kidney disease (CKD). J Clin Endocrinol Metab. 2012;97(10):3622–9. doi:10.1210/jc.2012-1411.
171. Watson B, Bergman SM, Myracle A, Callen DF, Acton RT, Warnock DG. Genetic association of 11 beta-hydroxysteroid dehydrogenase type 2 (HSD11B2) flanking microsatellites with

essential hypertension in blacks. Hypertension. 1996;28(3):478–82. http://www.ncbi.nlm.nih.gov/pubmed/8794836. Accessed 2 Mar 2014.
172. Whorwood CB, Ricketts ML, Stewart PM. Epithelial cell localization of type 2 11 beta-hydroxysteroid dehydrogenase in rat and human colon. Endocrinology. 1994;135(6):2533–41. doi:10.1210/endo.135.6.7988441.
173. Zhang M-Z, Xu J, Yao B, et al. Inhibition of 11beta-hydroxysteroid dehydrogenase type II selectively blocks the tumor COX-2 pathway and suppresses colon carcinogenesis in mice and humans. J Clin Invest. 2009;119(4):876–85. doi:10.1172/JCI37398.
174. Smith RE, Maguire JA, Stein-Oakley AN, et al. Localization of 11 beta-hydroxysteroid dehydrogenase type II in human epithelial tissues. J Clin Endocrinol Metab. 1996;81(9):3244–8. doi:10.1210/jcem.81.9.8784076.
175. Shimojo M, Ricketts ML, Petrelli MD, et al. Immunodetection of 11 beta-hydroxysteroid dehydrogenase type 2 in human mineralocorticoid target tissues: evidence for nuclear localization. Endocrinology. 1997;138(3):1305–11. doi:10.1210/endo.138.3.4994.
176. Perogamvros I, Keevil BG, Ray DW, Trainer PJ. Salivary cortisone is a potential biomarker for serum free cortisol. J Clin Endocrinol Metab. 2010;95(11):4951–8. doi:10.1210/jc.2010-1215.
177. Bocchi B, Kenouch S, Lamarre-Cliche M, et al. Impaired 11-beta hydroxysteroid dehydrogenase type 2 activity in sweat gland ducts in human essential hypertension. Hypertension. 2004;43(4):803–8. doi:10.1161/01.HYP.0000121362.64182.ad.
178. Ulick S, Levine LS, Gunczler P, et al. A syndrome of apparent mineralocorticoid excess associated with defects in the peripheral metabolism of cortisol. J Clin Endocrinol Metab. 1979;49(5):757–64. doi:10.1210/jcem-49-5-757.
179. Stewart PM, Corrie JE, Shackleton CH, Edwards CR. Syndrome of apparent mineralocorticoid excess. A defect in the cortisol-cortisone shuttle. J Clin Invest. 1988;82(1):340–9. doi:10.1172/JCI113592.
180. Stewart PM, Krozowski ZS, Gupta A, et al. Hypertension in the syndrome of apparent mineralocorticoid excess due to mutation of the 11 beta-hydroxysteroid dehydrogenase type 2 gene. Lancet. 1996;347(8994):88–91. http://www.ncbi.nlm.nih.gov/pubmed/8538347. Accessed 12 Feb 2014.
181. Stewart PM, Wallace AM, Valentino R, Burt D, Shackleton CH, Edwards CR. Mineralocorticoid activity of liquorice: 11-beta-hydroxysteroid dehydrogenase deficiency comes of age. Lancet. 1987;2(8563):821–4. http://www.ncbi.nlm.nih.gov/pubmed/2889032. Accessed 12 Feb 2014.
182. Tomlinson JW, Draper N, Mackie J, et al. Absence of Cushingoid phenotype in a patient with Cushing's disease due to defective cortisone to cortisol conversion. J Clin Endocrinol Metab. 2002;87(1):57–62. doi:10.1210/jcem.87.1.8189.
183. Morgan SA, McCabe EL, Gathercole LL, Hassan-Smith ZK, Larner DP, Bujalska IJ, Stewart PM, Tomlinson JW, Lavery GG. 11β-HSD1 is the major regulator of the tissue-specific effects of circulating glucocorticoid excess. Proc Natl Acad Sci USA. 2014;111(24):E2482-91. doi: 10..1073/pnas.1323681111
184. Cooper MS, Syddall HE, Fall CHD, et al. Circulating cortisone levels are associated with biochemical markers of bone formation and lumbar spine BMD: the Hertfordshire Cohort Study. Clin Endocrinol (Oxf). 2005;62(6):692–7. doi:10.1111/j.1365-2265.2005.02281.x.
185. Overman RA, Yeh J-Y, Deal CL. Prevalence of oral glucocorticoid usage in the United States: a general population perspective. Arthritis Care Res (Hoboken). 2013;65(2):294–8. doi:10.1002/acr.21796.
186. Fardet L, Flahault A, Kettaneh A, et al. Corticosteroid-induced clinical adverse events: frequency, risk factors and patient's opinion. Br J Dermatol. 2007;157(1):142–8. doi:10.1111/j.1365-2133.2007.07950.x.