11β-Hydroxysteroid Dehydrogenase Type 1 and Its Role in the Hypothalamus-Pituitary-Adrenal Axis, Metabolic Syndrome, and Inflammation

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Context: 11β-Hydroxysteroid dehydrogenase (11β-HSD) enzymes are now appreciated to be important regulators of hormone action at a tissue level. 11β-HSD1 is widely expressed and increases glucocorticoid action through its unique ability to convert inactive glucocorticoids (cortisone in man, 11-dehydrocorticosterone in rodents) to their active forms (cortisol and corticosterone, respectively). The enzyme has roles in the normal hypothalamus-pituitary-adrenal (HPA) axis, has been implicated in metabolic syndrome, and may modulate various aspects of the immune response.

Evidence Acquisition: A review of published, peer-reviewed medical literature (1990 to June 2009) on the physiology and pathophysiology of 11β-HSD1 was performed with an emphasis on HPA axis consequences, the metabolic syndrome, and the inflammatory response.

Evidence Synthesis: Studies of patients with genetic defects in 11β-HSD1 action show abnormal HPA axis responses with hyperandrogenism being a major consequence. The mechanisms underlying these abnormalities have been explored in mouse models with targeted deletion of components of the 11β-HSD1 system. A range of experimental studies emphasize the role of 11β-HSD1 in the metabolic syndrome and the potential for treatment with chemical inhibitors. An emerging area is the role of 11β-HSD1 in the inflammatory response.

Conclusions: 11β-HSD1 activity is an important component of the HPA axis and contributes to the metabolic syndrome and the normal immune response. Ongoing clinical observations and the development of selective inhibitors will further clarify the role of 11β-HSD1 in these areas. (J Clin Endocrinol Metab 94: 4645–4654, 2009)
apparent mineralocorticoid excess (5, 6). A wider role in human hypertension and cardiovascular disease is highlighted in recent articles (7–9).

11β-HSD1 is expressed constitutively in a range of tissues including the liver, adipose tissue, bone, and the central nervous system (10–12) but also has inducible expression in many other tissues including fibroblasts, skeletal and smooth muscle, and immune cells (13–16). In the majority of tissues, 11β-HSD1, although potentially bidirectional, functions predominantly as a reductase (1).

The hypothalamus-pituitary-adrenal (HPA) axis

Insights from monogenic disorders of 11β-HSD1 action

A number of patients have been identified with the putative 11β-HSD1-deficient state, cortisol reductase deficiency, but the determination of the genetic basis for this disorder has been a much more complicated story. These patients have impaired capacity to generate cortisol from an ingested dose of cortisone acetate, indicating lack of 11β-HSD1 reductase activity in the liver, and also have a urinary corticosteroid metabolite profile that is heavily biased toward the presence of cortisone relative to cortisol metabolites (a pattern that contrasts sharply with apparent mineralocorticoid excess) (17, 18). Without an increase in the activity of the HPA axis, the failure to generate cortisol from cortisone would lead to reduced levels of cortisol in the circulation (illustrated in Fig. 2B). This increase in HPA axis activation, however, is at the expense of an increase in adrenal androgen secretion, and it is this feature that often leads to the clinical presentation either through androgenization in women or premature adrenarche in either sex. Despite the phenotype clearly indicating a defect in 11β-HSD1, several studies failed to find mutations in the HSD11B1 gene leading to the condition being termed apparent cortisone reductase deficiency (ACRD) (17, 18). A major recent breakthrough has been the identification of a cofactor generating system that is physically associated with the 11β-HSD1 enzyme (19, 20). 11β-HSD1 is located in the endoplasmic reticulum (ER) of the cell, an intracellular compartment characterized by a high ratio of nicotinamide adenine dinucleotide phosphate in its reduced form (NADPH) relative to its oxidized form (NADP). This high ratio appears to be maintained by an enzyme called hexose-6-phosphate dehydrogenase (H6PDH), which converts glucose-6-phosphate (G6P) to 6-phosphogluconolactone in a reaction that regenerates NADPH from NADP (21, 22). Mutations of H6PDH have now been shown to form the basis for ACRD in several individuals (23). These cases are typified by a very low ratio of cortisol to cortisone metabolites, and it is likely that this is due to the continuing presence of the 11β-HSD1 enzyme but acting primarily as a dehydrogenase, inactivating rather than generating cortisol.

Insights from animals with targeted deletion of 11β-HSD1 or H6PDH

Mice with targeted disruption of either 11β-HSD1 or H6PDH have also been characterized. 11β-HSD1 knock-
out animals are phenotypically grossly normal (24). They lack 11β-HSD1 reductase activity, confirming that 11β-HSD1 is the only enzyme capable of generating substantial amounts of cortisol from cortisone in vivo. On some genetic backgrounds, there are abnormalities of the regulation of the HPA axis, with a high basal level of corticosterone, but on other backgrounds HPA axis responses are similar to wild type (12, 25). Strains that have a normal HPA axis appear to compensate by increasing hippocampal glucocorticoid receptor expression levels (25). In keeping with an impaired peripheral production of corticosterone, these animals also have an increase in the size of their adrenal glands.

H6PDH knockout mice express normal levels of 11β-HSD1 but have a change in directionality of the 11β-HSD1 enzyme such that it favors the dehydrogenase reaction in keeping with the ACRD clinical phenotype (26). This has been demonstrated by a change in the urinary metabolite excretion profile, with a shift to a reduced production of corticosterone compared with dehydrocorticosterone metabolites. Isolated tissue samples also clearly demonstrate this change in enzyme directionality. H6PDH knockout mice also had abnormalities of the corticosterone diurnal rhythm, with ACTH and corticosterone levels being elevated relative to wild-type animals, particularly at the nadir of the diurnal rhythm (27). There is also a significant increase in adrenal gland size due to the increased production of ACTH.

An interesting phenotype in these mice, which appears to differ from the phenotype seen in human H6PDH deficiency (ACRD), is the development of a progressive myopathy. The reason for this is currently unclear, but it is possible that a reduced ability to generate NADPH within the lumen of the ER could have an adverse effect on other ER reactions e.g. ER stress, unfolded protein response (28)] that occur in this compartment. This compartment is particularly specialized in muscle (in which it is referred to as the sarcoplasmic reticulum) and is involved in excitation-contraction coupling (29).

Because H6PDH activity determines the directionality of 11β-HSD1 activity, it is possible that factors that independently affected H6PDH might themselves regulate 11β-HSD1. To generate NADPH from NADP, H6PDH primarily converts G6P to 6-phosphogluconolactone (Fig. 1). The amount of G6P could thus influence the activity of H6PDH. This hypothesis has recently been tested in clinical situations in which there is an excess or deficiency of G6P. Glycogen storage disease (GSD) type 1 is caused by deficient activity of glucose-6-phosphatase (G6Pase), the rate limiting enzyme in gluconeogenesis. GSD1a is caused by deficiency of the G6Pase enzyme, which resides within the ER lumen, whereas GSD1b is caused by deficiency of the G6P transporter that enables G6P to enter the ER from the cytoplasm (30). Both conditions cause fasting hypoglycemia, and GSD1b has additional features such as neutrophil dysfunction. These two types of GSD are characterized by high and low levels of G6P within the ER respectively. It was shown using mouse models that high G6P levels (due to loss of G6Pase) altered the directionality of 11β-HSD1 in favor of corticosterone generation, whereas low G6P levels (due to loss of G6P transporter function) favored generation of dehydrocorticosterone from corticosterone (31). Studies of humans with GSD1a and -1b demonstrated equivalent abnormalities in 11β-HSD1 activity. GSD1a patients have an increased ratio of oxo to keto metabolites of cortisol and a greatly enhanced hepatic conversion of an oral dose of cortisone to cortisol, findings that indicate an increase in the enzymatic set point toward generation of active glucocorticoids. GSD1b patients had reduced ability to generate active glucocorticoids. Patients with GSD1a also had a reduction in the total amount of corticosteroids excreted, implying that the drive to adrenal corticosteroid production is reduced.

GSD is rare, but these results also have implications for hyperglycemia and diabetes. G6P levels are increased by hyperglycemia, and this high G6P level could then drive an increase in cortisone to cortisol conversion. Such an effect is supported by an increase in 11β-HSD1 reductase activity seen 3 h after a mixed meal (32). This effect has to be considered when interpreting data relating to the effect of 11β-HSD1 in the metabolic syndrome.

11β-HSD1 and the metabolic syndrome

Dysregulation of glucocorticoid action has been proposed to be a central feature of the metabolic syndrome (33). States of glucocorticoid excess recapitulate almost all features of the metabolic syndrome, but Cushing’s disease is rare and the circulating level of cortisol is normal in the vast majority of patients with obesity and type 2 diabetes.

We have raised the possibility that these features could be due to an increase in locally available glucocorticoids through 11β-HSD1 (11, 17, 34). Subsequently a range of studies explored the role of 11β-HSD1 in the pathogenesis of components of the metabolic syndrome including obesity, insulin resistance, hyperglycemia, and hyperlipidemia (Fig. 3).

11β-HSD1 and fat

11β-HSD1 activity was linked to the development of visceral obesity on the basis of observations that adipose stromal cells taken from human omental tissue had higher levels of 11β-HSD1 activity than those from subcutaneous fat (11). This activity, and the differentiation of preadipocytes to adipocytes, was stimulated by glucocorticoids suggesting...
that visceral adipose 11β-HSD1 expression could drive central obesity. Mice with transgenic overexpression of 11β-HSD1 in mature adipocytes (driven by the aP2 promoter) develop central obesity and recapitulate other features of the metabolic syndrome such as dyslipidemia and insulin resistance (35). Conversely, animals with artificially targeted expression of 11β-HSD2 in visceral fat, which inactivates glucocorticoid generation in this tissue, have a reduction in adipose tissue deposition on high-fat feeding (36).

Whereas these data do suggest a link between 11β-HSD1 overexpression, adipocyte differentiation, and visceral obesity, data obtained in humans have been more difficult to interpret. Studies examining the relationship between 11β-HSD1 mRNA expression and activity in biopsies or microdialysis of sc adipose tissue generally support a positive association with overall measures of fat mass such as body mass index (BMI) (37–42). The data with regard to omental fat are conflicting. A study of 32 women undergoing elective abdominal surgery failed to show a difference in adipocyte 11β-HSD1 activity or whole-tissue mRNA expression between obese and nonobese subjects (43). A negative correlation was seen between activity of preadipocytes cultured ex vivo and BMI. By contrast, a study of 21 women undergoing tubal ligation found positive associations of 11β-HSD1 with activity in intact fragments of human omental fat and BMI or visceral fat mass (45, 46).

No correlation between 11β-HSD1 mRNA expression and measures of adiposity were apparent. In the study by Lee et al. (45), the increased activity was thought to be due to differences in cofactor generation by H6PDH. The reason for the difference in the study by Veilleux et al. (46) could not be explained by this because activity was measured using a technique that did not require endogenous H6PDH activity. Perhaps the most consistent observation in these studies is the positive association between 11β-HSD1 expression and omental cell size. The differences in results are likely to relate to differences in the particular fat depot examined (e.g., sc vs. omental), whether preadipocytes or mature adipocytes are examined, evaluation of mRNA vs. protein, the type of enzyme assay used (intact cells vs. homogenates), and the confounding effects of insulin resistance and dietary composition (47–49). Other cell types present within adipose tissue such as macrophages also make a contribution to 11β-HSD1 activity (50). Although this effect appears minor compared with adipocytes (45), it could contribute to differences in expression between individuals. Further adding to the complexity, obesity-prone rodents were found to have reduced 11β-HSD1 activity in fat tissue relative to their lean counterparts (51, 52). Additionally, 11β-HSD1 expression within adipocytes is affected by acute changes in weight. Obese patients who were tested before and after substantial (>10% body weight) weight loss showed a significant increase in 11β-HSD1 expression in adipocytes (53). Likewise, adipose tissue expression of 11β-HSD1 in rodents fed a high-fat diet decreased despite weight gain (54). A critical experiment that should shed additional light on the role of 11β-HSD1 in visceral obesity will be the effect of enzyme inhibitors on visceral fat mass.

A role for 11β-HSD1 in exacerbating insulin resistance and diabetes mellitus has also been proposed (34, 55, 56). It is well known that excess glucocorticoids increase insulin resistance and can, in susceptible individuals, precipitate diabetes. Animals with targeted deletion of 11β-HSD1 appear to resist the development of insulin resistance in response to high-fat feeding (57). Additionally, specific 11β-HSD1 inhibitors have been shown to improve insulin sensitivity in animal models of the metabolic syndrome (58, 59). In humans, trials using carbadoxolone, a well-established nonspecific liquorice-based inhibitor of 11β-HSD enzymes, demonstrated improved insulin sensitivity (34). This effect is almost certainly due to effects on 11β-HSD1 activity, suggesting that specific inhibitors of the enzyme are likely to have the same effect.

The first data using a selective 11β-HSD1 inhibitor in the treatment of type 2 diabetes have recently been reported in abstract form (60). This randomized, placebo-controlled study involved the treatment of more than 300 obese men and women with type 2 diabetes who had failed metformin monotherapy. Over 12 wk, 100 and 200 mg of compound INCB13739 led to a significant reduction in

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FIG. 3. Schematic illustration of the role of the 11β-HSD1 enzyme in the metabolic syndrome.

- **Liver Tissue**: Expressed at high levels. Promotes gluconeogenesis, steatosis, and hypertriglyceridemia. Inhibition improves insulin sensitivity and/or weight gain and/or insulin resistance.

- **Adipose Tissue**:
  - **Visceral**: Promotes adipocyte differentiation and size. No net production of glucocorticoids in human studies.
  - **Subcutaneous**:
    - Expression with TNFα
    - Expression with IL2-IFNγ

- **Vascular Tissue**: Inhibition reduces progression of atherosclerosis in mice.
  - Expression in vascular smooth muscle in vitro but not in vivo.
  - Candidate of oxysterol metabolism and can compete with glucocorticoids.

- **Muscle**: Expression proposed to protect against insulin resistance.
  - Expression in rodent models of diabetes.

- **Pancreatic Islets**: Expression in β- and α-cells.
  - Leptin insulin and glucagon secretion.

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hemoglobin A1c and fasting plasma glucose. Beneficial effects were also seen on measures of insulin resistance and total cholesterol levels.

11β-HSD1 and liver

Conflicting observations have been made regarding the links between 11β-HSD1 expression and activity and insulin resistance in humans with the metabolic syndrome. Most studies suggest that 11β-HSD1 expression and activity in the liver is down-regulated in obesity (38, 61). This down-regulation, however, appears to be defective in individuals who are insulin resistant (56). The failure to down-regulate hepatic 11β-HSD1 could contribute further to insulin resistance and on the basis that glucocorticoids stimulate lipid production, exacerbating dyslipidemia. These relationships are complicated by the expression of additional glucocorticoid metabolizing enzymes in the liver, most importantly the A-ring reductases (5α- and 5β-reductase) (49, 62). The expression of these enzymes also appears to be associated with insulin resistance and, in a similar manner to 11β-HSD1, show a pattern of down-regulation with increased adiposity and insulin resistance.

A possible mediator of the hepatic changes seen in the metabolic syndrome, e.g. insulin sensitivity, could be increased production of cortisol from visceral fat in obesity. This increased cortisol would subsequently drain through the portal circulation to the liver. However, recent studies examining cortisol and cortisone levels in portal, and hepatic vein blood samples indicated that cortisol production from visceral adipose tissue, and thus the amount of exposure of the liver, does not significantly change with increasing obesity (63, 64).

11β-HSD1 and muscle

Another tissue in which a relationship between 11β-HSD1 and insulin resistance might be important is skeletal muscle. Human skeletal muscle cells express 11β-HSD1, and this activity is down-regulated by insulin in vitro, an effect proposed to be an autoprotective mechanism protecting muscle against insulin resistance (65). Muscle 11β-HSD1 activity has been reported to be decreased in diabetic subjects but is increased in a rat model of type 2 diabetes (66).

11β-HSD1 and pancreas

11β-HSD1 has also been proposed to have effects on insulin secretion itself. Expression has been reported in pancreatic β-cells, and in rodents, the local generation of corticosterone from dehydrocorticosterone reduced insulin release (67). A more recent report found a similar effect of dehydrocorticosterone on insulin release, but it appeared that enzyme expression was absent in β-cells, with this effect being mediated indirectly through expression within α-cells (68). This α-cell expression additionally inhibited insulin stimulated glucagon secretion.

11β-HSD1 and the vasculature

Atherosclerosis is clearly a major adverse consequence of the metabolic syndrome, but an independent role of 11β-HSD1 in the progression of atherosclerosis has also been proposed. In an experimental animal prone to the development of atherosclerotic lesions (apolipoprotein E knockout mice), a specific 11β-HSD1 inhibitor was able to substantially reduce (by ~84%) the development of atherosclerotic plaques (59). This effect was much greater than expected just from this inhibitor effect on other metabolic features such as dyslipidemia that could indirectly affect development of atherosclerosis. The mechanism for this is not clear. Experiments in mice do indicate the presence of 11β-HSD1 expression within the vasculature in vivo (15, 69, 70). The most comprehensive analysis reported 11β-HSD1 expression within the vascular smooth muscle, whereas 11β-HSD2 was expressed in the vascular endothelium (70). Induction of 11β-HSD1 by inflammatory cytokines is seen in vascular smooth muscle in vitro, providing a possible link with atherosclerosis, but induction by inflammation or injury does not appear to occur in vivo (71). A possible role for 11β-HSD1 activity in oxysterol metabolism has been proposed and the enzyme shown to be able to convert 7-ketocholesterol to 7β-hydroxycholesterol (72, 73). It is possible that this, or a related cholesterol modifying activity, could be involved with the progression of atherosclerotic pathways. Additionally, in an adipocyte cell line, high concentrations of oxysterols were able to compete with glucocorticoids, thus suggesting that oxysterols could act as endogenous inhibitors of tissue glucocorticoid metabolism (74).

Inflammation

The importance of glucocorticoids in the immune response is clear from both states of glucocorticoid excess and deficiency (75). Immune cells and tissues are, in general, highly sensitive to glucocorticoids. Glucocorticoids affect the migration of immune cells, their differentiated function, and the production of a range of inflammatory cytokines (76). The increase in circulating glucocorticoid levels through increased HPA axis activity is a key factor in the adaptive stress-inflammatory response (77). There is now evidence that glucocorticoid metabolism through the 11β-HSD enzymes provides an additional level of regulation during stress (78). This has been reported to be important in altering the glucocorticoid levels within specific target cells and tissues (Fig. 4).
Monocytes/macrophages

11β-HSD1 is expressed at low levels in circulating monocytes (14, 79). This expression increases substantially on differentiation to macrophages or dendritic cells in in vitro experiments. Expression in macrophages is stimulated further by IL-4 and IL-13 (examples of Th2 cytokines). Expression of 11β-HSD1 in resident macrophages is detectable in vivo in the mouse, and the activity increases very rapidly during the development of peritonitis (80). This increase in activity appears to be due to increased activity in cells migrating into the peritoneum in response to inflammation rather than to a change in the expression in resident cells. The time course for the increase in activity appears very different in these settings, with increases with monocyte differentiation occurring over days and in infiltrating phagocytes within hours so the mechanisms of induction are likely to be distinct. The expression of 11β-HSD1 in macrophages has been shown to be important in the early induction of the capacity of these cells to phagocytose apoptotic neutrophils (80). This suggests that glucocorticoid production via 11β-HSD1 can have a very active role in enhancing antiinflammatory/proresolution responses and is not solely due to reduction in lymphocyte function or the expression of proinflammatory cytokines. This concept is further supported by observations with a murine macrophage cell line in which 11β-HSD1 inhibitors were able to attenuate the production of proinflammatory cytokines in response to lipo-polysaccharide treatment (50).

The notion that macrophages express 11β-HSD1, which functions to fine-tune immune responses or hasten their resolution, seems biologically plausible. A more provocative and controversial finding is the expression of the 11β-HSD2 enzyme in circulating and tissue monocytes/macrophages in patients with rheumatoid arthritis (RA) (81–84). These findings are based on gene expression arrays which identify 11β-HSD2 expression as one of the genes most up-regulated in monocytes in early RA (82, 83). Expression of 11β-HSD2 has also been described in synovial tissue from patients with RA (82, 84). This issue needs further study because expression of 11β-HSD2 in macrophages would be expected to render them insensitive to prednisolone and prednisone, the oral glucocorticoids most commonly used to treat RA (85). These findings do, however, illustrate how aberrant expression of 11β-HSD enzymes in disease states could potentially dramatically change the nature of the immune response.

Lymphocytes/lymphoid tissue

11β-HSD1 is also expressed, at least under certain circumstances, in most lymphocyte populations (86). Resting CD4- and CD8-positive T cells and B cells isolated from mice express 11β-HSD1 in which it functions exclusively as a reductase. This activity increased further when naive CD4-positive cells were activated by T cell receptor stimulation or when the cells were differentiated in vitro into Th1 or Th2 subtypes. Intracellular generation of active glucocorticoids from inactive precursors was associated with a reduction in cytokine production, an effect that did not occur in cells obtained from an 11β-HSD1 knockout mouse. Interestingly, the expression of 11β-HSD1 in lymphocytes increases with age (at least in mice), and suggests a potential role for increasing 11β-HSD1 in the well-established decline in the immune response with aging. The expression of 11β-HSD1 is also seen in the thymus (88). Thymocytes express low levels of 11β-HSD1, but this increases substantially in an experimental burn injury model in mice, an effect that is associated with an increased rate of thymocyte apoptosis.

Stromal response to inflammation

Proinflammatory mediators can induce 11β-HSD1 in a range of nonimmune cells and tissues that do not normally express significant amounts of the enzyme. This effect has been demonstrated in glomerular mesangial cells, adipocytes, osteoblasts, myoblasts, fibroblasts, vascular smooth muscle, and ovarian surface epithelial cells (10, 13, 15, 89–91). Increases in 11β-HSD1 expression at a tissue level in inflammatory states have been demonstrated in synovial and colonic tissue (84, 92). The inflammatory mediators have mostly been TNFα and/or IL-1β and to a lesser extent the Th2 cytokines IL-13 and IL-4. The induction of 11β-HSD1 activity has been shown to have functional effects on the cells themselves but is likely to also increase glucocorticoid levels within the tissue itself. This has been
shown in the synovium in which the increased expression in response to inflammation was proposed to reflect an attempt to reduce inflammation within the joint (84). Interestingly, the effect of proinflammatory cytokines on induction of 11β-HSD1 was further enhanced by glucocorticoids themselves in both synovial fibroblasts and primary osteoblasts, indicating that high glucocorticoid levels, rather than inhibiting the action of proinflammatory cytokines, will reinforce their action to increase tissue cortisol levels (93). In such tissues it is likely that the high local glucocorticoid levels could impair the function of immune cells that migrate into the joint, even if they themselves do not express 11β-HSD1.

These findings suggest that 11β-HSD1 expression plays a dynamic role in the regulation of the inflammatory response by initially influencing the differentiation and function of antigen presenting cells and the effectors of innate immunity and then subsequently influencing the tissue level of active glucocorticoids through effects on stromal cells.

**Clinical use of 11β-HSD1 inhibitors**

A range of inhibitors of 11β-HSD1 for potential clinical use are in development (58, 59, 94, 95), and recent patent activity in this area has recently been reviewed (96). Several inhibitors have been evaluated in rodent models and some are now being tested in humans. Most inhibitors directly inhibit the 11β-HSD1 enzyme independently of interactions with its cofactors, but there is the possibility that some will preferentially bind to the enzyme bound to either cofactor (97, 98). This theoretically could lead to inhibitors that preferentially inhibit the reductase or dehydrogenase reaction.

Inhibitors could potentially have beneficial effects in a range of diseases. The main conditions currently being examined are diabetes and the metabolic syndrome, but they also could have a role in the treatment of osteoporosis and cognitive decline (87, 99). A potential issue related to the use of these inhibitors is that they could reduce the degree of systemic generation of cortisol from cortisone an effect that would, as described above, lead to stimulation of the HPA axis (Fig. 3). This could lead to problematic hyperandrogenism in women (a feature that is difficult to examine in rodent models because they do not secrete significant amounts of adrenal androgens). This reduced capacity to generate active glucocorticoids will also mean that these patients will be unresponsive to therapeutic glucocorticoids if they are given in the precursor form (cortisone and prednisone) but should maintain sensitivity to hydrocortisone (cortisol) and prednisolone because these steroids do not need first pass metabolism by 11β-HSD1 for their activity. The limited data in humans treated with a selective 11β-HSD1 inhibitor demonstrated an increase in ACTH levels during treatment, but cortisol levels did not change (60). Adrenal androgen levels also increased, but the mean value for the treated groups was still within the normal sex adjusted range. Given the inducible expression of 11β-HSD1 in inflammation, there is clearly the possibility that these drugs could influence inflammatory responses, and this needs to be borne in mind as an additional potential drawback of therapy. Reassuringly, data from transgenic animals with deletion of 11β-HSD1 and the experience with patients with genetic impairment of 11β-HSD1 activity have not yet suggested that this is likely to be a problem in all but the most severe of inflammatory states.

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