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Minireview: 11β-Hydroxysteroid Dehydrogenase Type 1—A Tissue-Specific Amplifier of Glucocorticoid Action*

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ABSTRACT

11β-hydroxysteroid dehydrogenases (11β-HSDs) catalyze the interconversion of active glucocorticoids (cortisol, corticosterone) and inert 11-keto forms (cortisone, 11-dehydrocorticosterone). 11β-HSD type 2 has a well recognized function as a potent dehydrogenase that rapidly inactivates glucocorticoids, thus allowing aldosterone selective access to otherwise nonselective mineralocorticoid receptors in the distal nephron. In contrast, the function of 11β-HSD type 1 has, until recently, been little understood. 11β-HSD1 is an ostensibly reversible oxidoreductase *in vitro*, which is expressed in liver, adipose tissue, brain, lung, and other glucocorticoid target tissues. However, increasing data suggest that 11β-HSD1 acts as a predominant 11β-reductase in many intact cells, whole organs, and *in vivo*. This reaction direction locally regenerates active glucocorticoids within expressing cells, exploiting the substantial circulating levels of inert 11-keto steroids. While the biochemical determinants of the reaction direction are not fully understood, insights to its biological importance have been afforded by use of inhibitors *in vivo*, including in humans, and the generation of knockout mice. Such studies suggest 11β-HSD1 effectively amplifies glucocorticoid action at least in the liver, adipose tissue, and the brain. Inhibition of 11β-HSD1 represents a potential target for therapy of disorders that might be ameliorated by local reduction of glucocorticoid action, including type 2 diabetes, obesity, and age-related cognitive dysfunction. (*Endocrinology* **142:** 1371–1376, 2001)

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GLUCOCORTICOIDS and mineralocorticoids, like other steroids, are lipophilic and readily access their intracellular receptors. Until a decade or so ago, it was thought that the main determinants of corticosteroid action were the levels of hormones in the blood, their binding by plasma proteins (*e.g.* corticosteroid binding globulin), and the varying densities of receptors in target tissues. However, it has become apparent that an additional and important level of control is exerted by pre-receptor metabolism of ligands by tissue-specific enzymes. Such modulation of steroid action by local metabolism has been described for other hormones, including androgens (5α-reductases), oestrogens (17β-hydroxysteroid dehydrogenases and aromatase), and thyroid hormones (5′-monodeiodinases). For glucocorticoids, the key enzymes are 11β-hydroxysteroid dehydrogenases (11β-HSDs). Understanding the tissue-specific functions of 11β-HSDs has led to new insights into pathophysiology of common diseases and has suggested novel approaches to target experimental and therapeutic manipulations of steroid action. Here we review the emerging biology of 11β-HSDs with emphasis on the hitherto rather neglected type 1 isozyme.

History

Almost 50 yr ago Amelung and colleagues (1), discovered the enzymic interconversion of active 11-hydroxy glucocorticoids (cortisol, corticosterone) and inert 11-keto forms (cortisone, 11-dehydrocorticosterone). This 11β-HSD activity was subsequently described in a broad range of cells and tissues. In the mid 1980s Monder and co-workers in New York purified an NADP(H)-dependent 11β-HSD activity from rat liver, which catalyzed both 11β-dehydrogenation of cortisol to inert cortisone and also the 11β-reduction of cortisone to active cortisol (2). At this stage, 11β-HSD was thought to represent one of several arcane pathways for clearance of glucocorticoids and no specific function was ascribed to it. However, in the late 1980s Edwards and colleagues in Edinburgh and Funder *et al.* in Melbourne (3, 4) recognized the key physiological importance of the inactivation of cortisol to cortisone. These workers discovered that 11β-HSD activity in the distal nephron could explain the mineralocorticoid receptor paradox. This arose from findings that purified or recombinant mineralocorticoid receptors were nonselective *in vitro* and bound the glucocorticoids cortisol and corticosterone with equal affinity to the physiological mineralocorticoid aldosterone (5). Nevertheless, the same receptors *in vivo* were aldosterone specific in the face of severalfold molar excess of glucocorticoid (6). The explanation lay in 11β-HSD, which rapidly inactivated glucocorticoids in aldosterone target cells in the distal nephron, thus allowing selective access of aldosterone to mineralocorticoid receptors. In the congenital absence of this activity (the syndrome of apparent mineralocorticoid excess) (7), or with liquorice-based inhibitors of 11β-HSD (8), glucocorticoids illicitly occupy mineralocorticoid receptors causing sodium retention, hypokalemia, and hypertension.

One or two isozymes of 11β-HSD?

Monder and colleagues then cloned a complementary DNA (cDNA) using antibodies raised against their 11β-HSD

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purified from rat liver (9). This cDNA hybridized with a product highly expressed in rat kidney (10) and was thought to represent the active 11β-dehydrogenase. However, it became clear that this enzyme could not explain mineralocorticoid receptor protection in the distal nephron. For example, it was expressed widely (including in hippocampus, where mineralocorticoid receptors are not selective for aldosterone), was of low affinity (micromolar K_m for active 11-hydroxysteroids), and did not match the regulation or cofactor preference of the 11β-dehydrogenase activity in distal nephron. These discrepancies were resolved with the purification (11) and cloning (12, 13) of a second isozyme, 11β-HSD2 (see Fig. 1).

11β-HSD2 is highly expressed in classical aldosterone-selective target tissues (distal nephron, colon, sweat glands) and the placenta. 11β-HSD2 cDNA encodes a high affinity, NAD-dependent dehydrogenase that rapidly inactivates glucocorticoids with a low nanomolar K_m. This enzyme has negligible 11β-reductase activity. Mutations in the 11β-HSD2 gene are seen in patients with the congenital syndrome of apparent mineralocorticoid excess (14). Mice homozygous for targeted disruption of the 11β-HSD2 gene (15) recapitulate the features of glucocorticoid-dependent mineralocorticoid excess. It is therefore quite clear that 11β-HSD2 is the enzyme responsible for protecting mineralocorticoid receptors from glucocorticoids *in vivo*. What then is the function of Monder's rat liver enzyme, 11β-HSD Type 1?

Modulation of Receptor Activation by 11β-HSD1

11β-HSD1 is widely expressed, most notably in liver, lung, adipose tissue, vasculature, ovary, and the central nervous system (CNS) (16, 17). High expression is also observed in the kidney and testis in the rat, but not in the mouse. In many of these sites there is negligible expression of mineralocorticoid receptors, but glucocorticoids play a key role in regulation of metabolism through activation of relatively low affinity glucocorticoid receptors. Might 11β-HSD1 have a role in modulating glucocorticoid access to these receptors? If so, would this attenuate or enhance glucocorticoid receptor activation?

11β-dehydrogenase or 11β-reductase?

In original purification studies, the 11β-HSD1 in the liver was shown to be bidirectional, although, in contrast with its dehydrogenase activity, the reductase activity was unstable *in vitro* (2). More recently, a series of studies suggest that the enzyme prefers the reductase direction unless cells are disrupted. This applies in primary cultures of cells from liver (18), adipose tissue (19), lung (20), CNS (21), and vascular smooth muscle (22). In a few studies, for example in Leydig cells, 11β-dehydrogenase activity has been reported in apparently intact cell preparations (23), but others have found predominant 11β-reduction (24) and argued that some 11β-HSD1 must be liberated from damaged cells to detect 11β-dehydrogenase activity. This striking change in directionality between intact cells and homogenates has never been satisfactorily explained, but may reflect the specific intracellular localization of 11β-HSD1 in the inner leaflet of the endoplasmic reticulum, where neighboring enzymes may be powerful generators of the reduced cosubstrate NADPH. Short-term post-translational changes such as enzyme phosphorylation may also be pertinent, particularly to the apparent instability of the 11β-reductase activity in homogenates, but remain to be investigated. Alternative explanations, such as longer-term posttranslational modifications (varying N-linked glycosylation) (25) would not explain why 11β-HSD1 activity is overwhelmingly reductive in intact cells and then shows predominant dehydrogenation in homogenates of these same cells.

These observations in cells suggested a novel role for 11β-HSD1, involving reactivation rather than inactivation of glucocorticoid. Does this occur in intact organs? Isolated perfused cat (26) or rat (27) liver models suggest that 11β-HSD1, which is the only isozyme expressed in the liver, is indeed a predominant 11β-reductase with a high capacity for reactivating 11-ketosteroid substrate over a broad range of substrate concentrations. These findings can be extrapolated to human liver *in vivo*, since historical work suggests that, on oral administration, cortisone (the first pharmacological glucocorticoid used in man) is rapidly activated to cortisol. Indeed, recent studies confirm that very little oral cortisone

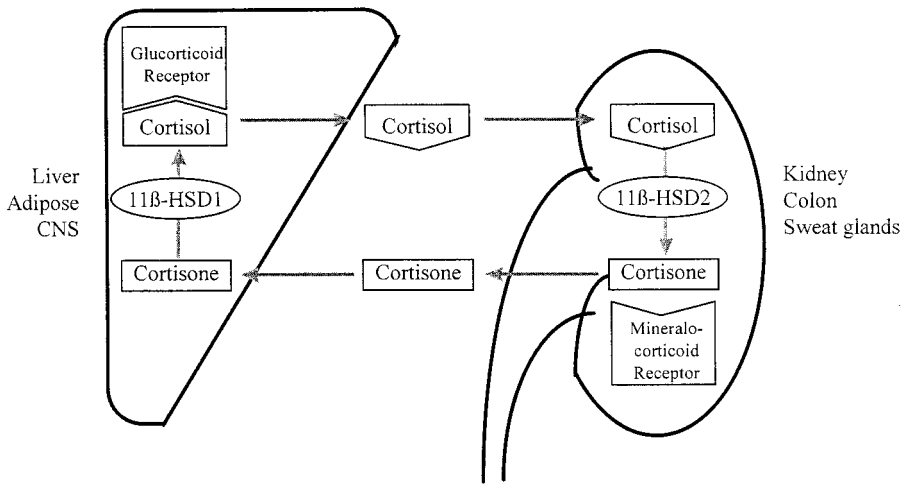

FIG. 1. Contrasting functions of the isozymes of 11β-HSD. 11β-HSD2 is an exclusive 11β-dehydrogenase that acts in classical aldosterone target tissues to exclude cortisol from otherwise nonselective mineralocorticoid receptors. Inactivation of cortisol also occurs in placenta. 11β-HSD1 is a predominant 11β-reductase *in vivo* that acts in many tissues to increase local intracellular glucocorticoid concentrations and thereby maintain adequate exposure of relatively low affinity glucocorticoid receptors to their ligand.

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reaches the systemic circulation (28) and that hepatic vein cortisol/cortisone ratios are very high (29). 11β-reductase activity has been shown in other human tissues *in vivo*, including sc adipose tissue (30).

Availability of substrate

So, 11β-HSD1 acts as a reductase to reactivate glucocorticoids in most, if not all, cells in which it is expressed *in vivo*. In order for this reactivation to play any physiological role in regulating receptor exposure (as opposed to a pharmacological role when cortisone is administered), there would need to be a substantial pool of substrate inert 11-ketosteroids available. The main source of 11-ketosteroid is 11β-HSD2, predominantly in kidney (31). In humans, cortisone circulates at levels around 50–100 nmol/liter, largely unbound to plasma proteins and without a pronounced diurnal rhythm (29). In contrast, cortisol is approximately 95% bound, largely to corticosteroid-binding globulin, giving "free" cortisol levels between approximately 1 nmol/liter at the diurnal nadir and approximately 100 nmol/liter during the diurnal peak and on stress. In the rat, plasma concentrations of 11-dehydrocorticosterone are also approximately 50 nmol/liter, though in the mouse levels are lower around 3–5 nmol/liter (32). Thus, for at least part of the day, circulating cortisone levels equal or exceed free cortisol levels and similar ratios pertain in rodents.

Evidence that 11β-HSD1 amplifies glucocorticoid action

Early studies had addressed the hypothesis that 11β-HSD1, like 11β-HSD2, was a predominant dehydrogenase enzyme, which protected glucocorticoid receptors, *e.g.* in testis (33). However, from the above, it appears that there is an ample supply of inert substrate that can be reactivated by predominant 11β-reductase activity of 11β-HSD1 in many tissues *in vivo*. What is the evidence that this influences local glucocorticoid receptor activation?

Liver. The most persuasive data that 11β-HSD1 increases effective intracellular glucocorticoid action have been obtained in liver. Here, glucocorticoids oppose the actions of insulin, for example, by up-regulating expression of the rate-limiting enzyme for gluconeogenesis, phosphoenol-pyruvate carboxykinase (PEPCK). In male rats, estradiol potently down regulates 11β-HSD1 expression (34) and, only in the presence of glucocorticoids, also down-regulates PEPCK expression (35). Such indirect studies, as well as the use of relatively nonselective liquorice-based inhibitors, indicate that impaired activity of 11β-HSD1 in liver is associated with features of reduced glucocorticoid action and increased insulin sensitivity in hepatocytes.

To explore this further, 11β-HSD1 knock-out mice have been generated (32). These mice appear to develop normally and are viable, fertile, and normotensive. This model shows that 11β-HSD1 is the sole major 11β-reductase, at least in mice, since adrenalectomized knockout mice cannot convert administered 11-dehydrocorticosterone to active corticosterone. However, despite slightly elevated basal plasma corticosterone levels (see below), 11β-HSD1 −/− mice have a phenotype compatible with impaired intracellular glucocorticoid regeneration and reduced antagonism of insulin action. For example, they show impaired induction of PEPCK and glucose-6-phosphatase on fasting and a lesser hyperglycemic response to stress or induction of obesity (32).

These findings are supported by experiments in healthy humans using the liquorice derivative carbenoxolone to inhibit 11β-HSD1 activity (36). This is similarly associated with enhanced insulin sensitivity, as measured in a euglycaemic hyperinsulinaemic clamp study, although it remains to be demonstrated whether this is due to altered glucose dynamics in liver and/or peripheral tissues such as adipose.

Brain. There is also good evidence that 11β-reductase modulates glucocorticoid action in brain. In the CNS, glucocorticoids regulate key developmental, metabolic, neurotransmitter and structural functions, particularly in neurons. Chronic glucocorticoid excess has deleterious effects most notably in the hippocampus, which has a very high density of receptors. 11β-HSD1 is highly expressed in hippocampus as well as other CNS regions (37). As elsewhere, 11β-HSD1 in hippocampal cells is a reductase, amplifying glucocorticoid action. Indeed, 11-dehydrocorticosterone is as potent as corticosterone in potentiating excitatory amino acid neurotoxicity *in vit*ro, an effect lost on inhibition of the enzyme (21). Use of liquorice-based inhibitors has not supported the notion that this reaction is important in hippocampal function/neuronal survival *in vivo* (38). However, such compounds penetrate the CNS rather patchily (39) and are relatively nonselective [*i.e.* inhibit both 11β-HSD isozymes, as well as other enzymes of steroid metabolism and even prostaglandin degradation (40)]. Preliminary studies in 11β-HSD1 null mice support the notion that the enzyme attenuates the deleterious effects of chronic glucocorticoid excess upon cognitive function (Yau *et al.*, 40a).

Expression of 11β-HSD1 in hippocampus, hypothalamus, and pituitary also suggests that it may influence negative feedback regulation of the hypothalamic-pituitary-adrenal axis (HPA) by endogenous glucocorticoids. 11β-HSD1 null mice have adrenocortical hypertrophy and increased responses of the adrenal to ACTH *in vitro* (32). This could be explained because they are unable to regenerate glucocorticoids in the periphery and hence have enhanced metabolic clearance rate. However, plasma levels of corticosterone are also modestly elevated at the diurnal nadir, findings suggestive of HPA axis activation over and above that required to compensate for altered peripheral clearance. Such effects might be due to either increased forward drive to the HPA axis and/or to attenuated glucocorticoid feedback control. Recent data suggest that this is, at least in part, due to blunted sensitivity to glucocorticoid feedback, since administration of a dose of cortisol that suppresses the HPA responses to a subsequent stressor in wild-type mice fails to do so in 11β-HSD1 null mice (41).

Other glucocorticoid targets. In some tissues, the role of 11β-HSD1 has been more difficult to establish because of nearby expression of 11β-HSD2. An example is in the blood vessel wall. Here, glucocorticoids and mineralocorticoids act on many targets to influence vascular responses. Early data showed expression of 11β-HSD1 in vascular smooth muscle

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(42) with potentiation of responses to glucocorticoids by liquorice derivatives (43), suggesting predominant 11β-dehydrogenase activity. However, 11β-HSD2 has recently been described in endothelial cells (44) where glucocorticoids influence nitric oxide generation (45). 11β-HSD1 knockout mice have normal vascular function, whereas 11β-HSD2 knockout mice have endothelial dysfunction. Whether reactivation of glucocorticoids by 11β-HSD1 in vascular smooth muscle offsets the influence of 11β-HSD2 in the endothelium remains to be established.

In many other tissues, descriptive studies suggest an association between 11β-HSD1 expression and the necessity for adequate exposure to glucocorticoids. These are not reviewed in detail here (see Refs. 16 and 17) but include ovarian granulosa cells, cells within the eye, stromal cells in the lymph node, and the lung.

Role of 11β-HSD1 in the coordinated control of metabolic function

Having established that 11β-HSD1 can modulate glucocorticoid action in key sites controlling metabolic fuel utilization, the next step will be to understand how these effects are regulated and integrated in the metabolic responses to environmental stimuli. In contrast with 11β-HSD2, which provides a constitutive barrier against glucocorticoid access to receptors, 11β-HSD1 expression is highly regulated. Factors influencing 11β-HSD1 expression and activity include glucocorticoids, thyroid hormones, sex steroids, GH, IGF-1, insulin, and cytokines. These are not reviewed in detail here (see Refs. 16 and 17). A clear synthesis of the physiological importance of these factors remains elusive, in part because studies of these processes have been hampered by variations between species and between tissues. However, several recent strands suggest that 11β-HSD1 has a place in coordinated metabolic control. For example, in the long term, chronic stress or elevated glucocorticoid levels appear to attenuate 11β-HSD activity (46), at least in liver and hippocampus. This might represent a homeostatic mechanism to reduce excessive metabolic effects of glucocorticoids during chronic stress, while maintaining exposure of other peripheral tissues (*e.g.* in the immune system) to elevated circulating glucocorticoid levels.

Very recent studies have attempted to elucidate the molecular basis for regulation of 11β-HSD1. In the rat, the promoter is predominantly regulated, at least in liver, by the C/EBP family of transcription factors (47), mainly C/EBPα. C/EBPα coordinately regulates a series of genes concerned with the metabolism of fuels and is in turn regulated by glucocorticoids. It has been suggested that such cross-talk allows C/EBPα to regulate not only its direct target genes but also to amplify glucocorticoid action, engendering a coordinate response to metabolic challenge (47). Similar pathway cross-talk may occur with other transcription factors. Thus, PPARα ligands, such as fibrates, attenuate 11β-HSD1 (48). This action may allow PPARα activators to reduce triglyceride levels both directly via PPARα target genes and indirectly via reduced 11β-HSD1 amplification of glucocorticoid target gene expression in liver. Such speculations remain to be directly analyzed. The basis of the tissue-specific responses of 11β-HSD1 to transcriptional and other regulation also remains a key target for determination.

11β-HSD1 in Human Disease

Glucocorticoid excess and deficiency produce the dramatic clinical features of Cushing's syndrome and Addison's disease, respectively. It has long been suspected that glucocorticoids contribute to the pathophysiology of more common disorders, including hypertension, obesity, and type 2 diabetes mellitus. Understanding the physiological role of 11β-HSDs has led clinical investigators to address the importance of prereceptor metabolism. Subtle deficiency of 11β-HSD2 may be important in some patients with essential hypertension (49, 50). The potential importance of 11β-HSD1 in pathophysiology and treatment has only been appreciated relatively recently.

A handful of patients with apparent congenital cortisone reductase deficiency have been described, but none has had mutations in the coding regions of the 11β-HSD1 gene (28, 51). This suggests that either another enzyme is responsible for the apparent loss of 11β-reductase or, more likely, that the deficit lies at the level of gene regulation. Mutations in promoter or intronic regions have not as yet been fully screened. Whatever the etiology, such patients show the predicted exaggerated HPA axis function with increased adrenal androgen production. Measurements of glucocorticoid responses in target tissues such as liver and fat have not been made.

Impaired 11β-HSD1 may also be important in more common clinical syndromes. In the leptin-resistant Zucker obese rat, 11β-HSD1 is impaired in liver, a change predicted to ameliorate the local intrahepatic metabolic consequences of the obesity (52). However, this may also activate the HPA axis to compensate for the increased clearance of glucocorticoids though reduced hepatic regeneration. It appears that similarly impaired hepatic 11β-HSD1 in liver occurs in patients with polycystic ovary syndrome (53) and primary obesity (54, 55).

An alternative possibility is that enhanced 11β-HSD1 is important in increasing local glucocorticoid action and promoting adverse metabolic effects. In the face of impaired 11β-HSD1 activity in liver, Zucker obese rats show selectively enhanced activity of 11β-HSD1 in omental adipose tissue (52). Very recent studies suggest the same tissue-specific pattern of dysregulation of 11β-HSD1 (*i.e.* impaired in liver, enhanced in adipose tissue) in human obesity (30, 55).

Finally, whether or not altered 11β-HSD1 is involved in the pathophysiology of a disorder, manipulation of enzyme activity may provide a means of manipulating glucocorticoid action in specific tissues without affecting circulating cortisol levels. For example, studies in rats show that 11β-HSD1 is down-regulated, at least in liver, by continuous (female pattern) GH administration (34). Administration of daily GH to hypopituitary patients also results in lower ratios of cortisol/cortisone metabolites consistent with inhibition of 11β-HSD1 (56). It is intriguing to think that a resultant lowering of intraadipose cortisol concentrations contributes to the reduction in body fat that accompanies GH therapy in these

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patients. Similarly, the observation that an inhibitor of 11β-HSD1, carbenoxolone, enhances insulin sensitivity in healthy volunteers (36) offers the tantalizing prospect that selective 11β-HSD1 inhibitors will be novel insulin-sensitizing agents.

Future Directions

The findings reviewed above suggest that 11β-HSD1, rather than being the Cinderella of the 11β-HSD sisters, may be the more intriguing and therapeutically important isozyme. If studies in null mice and with nonselective inhibitors are correct, inhibitors of 11β-HSD1 might increase insulin sensitivity in liver and fat and even reduce the deleterious aging effects of chronic glucocorticoid exposure in the CNS (cognitive impairment, dementia). Such work requires the development of selective inhibitors that do not interfere with other enzymes, particularly 11β-HSD2. However, it is also clear that a number of issues need to be resolved.

It will be important to determine what are the major controls of enzyme reaction direction *in vivo* since swinging the balance between reduction and dehydrogenation might be an alternative approach to manipulating tissue glucocorticoid levels. A key step will be to obtain a crystallographic structure for the enzyme and understand its interactions with substrates and cofactors. It is also crucial to work out the molecular basis for tissue-specific regulation of 11β-HSD1. The potential to manipulate this enzyme in a tissue-specific manner opens up intriguing investigational and therapeutic possibilities. The role of 11β-HSD1, notably at the tissue-specific level, requires to be dissected in humans. Current measures of overall enzyme activity using GC-MS estimations of urinary metabolites are blunt, and removing cells into culture is anticipated *per se* to alter enzyme expression and potentially kinetics. Finally, studies of 11β-HSD1 gene structure, polymorphisms and haplotypes will perhaps help explain heterogeneity of activity and regulation in the population.

This review illustrates how fundamental observations during the last 5 yr have been applied rapidly in physiological and pharmacological studies of 11β-HSD1. The next 5 yr will likely reveal just how complex and valuable the 11β-HSD system may be.

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