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Review

11β-Hydroxysteroid dehydrogenase 1: Regeneration of active glucocorticoids is only part of the story

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ABSTRACT

11β-Hydroxysteroid dehydrogenase 1 (11β-HSD1) is an endoplasmic reticulum membrane enzyme with its catalytic site facing the luminal space. It functions primarily as a reductase, driven by the supply of its cosubstrate NADPH by hexose-6-phosphate dehydrogenase (H6PDH). Extensive research has been performed on the role of 11β-HSD1 in the regeneration of active glucocorticoids and its role in inflammation and metabolic disease. Besides its important role in the fine-tuning of glucocorticoid action, 11β-HSD1 is a multi-functional carbonyl reductase converting several 11- and 7-oxosterols into the respective 7-hydroxylated forms. Moreover, 11β-HSD1 has a role in phase I biotransformation reactions and catalyzes the carbonyl reduction of several non-steroidal xenobiotics. Recent observations from experiments using selective inhibitors and studies with transgenic mice indicated a role for 11β-HSD1 in oxysterol metabolism and in bile acid homeostasis, with evidence for glucocorticoid-independent effects on gene expression. This review focuses on the promiscuity of 11β-HSD1 to accept structurally distinct substrates and discusses recent progress mainly on non-glucocorticoid substrates.

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Contents

1. Introduction

Glucocorticoids are essential endocrine hormones involved in the regulation of almost all major physiological functions, including energy metabolism, cell proliferation and differentiation, reproduction, immune system, and cardiovascular and brain function. Upon the loss of adrenal glucocorticoid production, without hormonal substitution, the human organism survives only for a couple of days, emphasizing its importance. Thus, disturbances of glucocorticoid homeostasis are linked with several major diseases such as osteoporosis, metabolic syndrome, cardiovascular complications, immune and psychiatric disorders [1,2]. The identification and characterization of the adrenal corticosteroid hormones and the discovery of the anti-inflammatory effects of the glucocorticoid cortisone in patients with rheumatoid arthritis was later honored by the Nobel Prize to Drs. Philip S. Hench, Edward C. Kendall and Tadeus Reichstein. This intensified the research on glucocorticoids and boosted the development of synthetic glucocorticoids; many of them are still widely used in therapy [2,3]. Glucocorticoids are of

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therapeutic value and they still belong to the most widely prescribed drugs. Interestingly, cortisone and the synthetic derivative prednisone, which is widely used as co-medication after organ transplantation [4], both are inactive by themselves and need to undergo metabolic activation (see Section 2).

During evolution, several mechanisms appeared that allow a fine-tuned regulation of glucocorticoid signaling and downstream effects. This includes two nuclear receptors with moderate and high affinity for glucocorticoids (*i.e.*, glucocorticoid receptor (GR) and mineralocorticoid receptor (MR)) and two short-chain dehydrogenase/reductase (SDR) enzymes (*i.e.*, 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1) and 11β-HSD2) that interconvert active (cortisol, corticosterone) and inactive glucocorticoids (cortisone, 11-dehydrocorticosterone).

11β-HSD2 is an endoplasmic reticulum (ER) membrane protein and acts exclusively as an oxidase on endogenous glucocorticoids, thereby playing an important role in the tissue-specific inactivation of glucocorticoids (recently reviewed in [5]). It utilizes NAD^+ as a cofactor and is expressed in mineralocorticoid target tissues such as kidney, colon and sweat glands where it serves to protect the MR from excessive activation by glucocorticoids, thereby rendering access of aldosterone to the receptor. 11β-HSD2 is also expressed in placenta to protect the fetus from high maternal glucocorticoids.

The ability of liver tissue homogenates to metabolize adrenal hormones has already been described in the 1950s [6]; however, 11β-HSD1 was finally purified from rat liver microsomes and cloned more than 30 years later [7,8]. Purified 11β-HSD1 and lysates expressing recombinant 11β-HSD1 exhibit both dehydrogenase and reductase activity [9]; however, in intact hepatocytes and macrophage the enzyme functions predominantly as a reductase [10]. Kinetic studies of 11β-HSD1 expressed in cultured cells using recombinant Vaccinia virus suggested that cofactor availability might determine the reaction direction of 11β-HSD1 [9]. The determination of the intracellular localization then revealed that 11β-HSD1 is an integral membrane enzyme of the ER with a lumenal orientation of its active site [11–13]. The subsequent identification of the luminal enzyme hexose-6-phosphate dehydrogenase (H6PDH) as a supplier of NADPH [14,15] provided an explanation for the reaction direction of 11β-HSD1 in intact cells. H6PDH catalyzes the first two steps of the pentose phosphate pathway in the ER and represents a major source of intraluminal NADPH. In contrast to the cytosolic glucose-6-phosphate dehydrogenase, H6PDH has a broader substrate specifity, not discriminating between glucose-6-phosphate, galactose-6-phosphate, 2-deoxyglucose-6-phosphate and other hexose-6-derivatives [16–19]. Nevertheless, it is believed that under physiological conditions, H6PDH utilizes glucose-6-phosphate as its main substrate [18]. The intraluminal substrate supply is maintained by a specific glucose-6-phosphate transporter [20]. The disruption of the functional cooperation between 11β-HSD1 and H6PDH upon tissue homogenization or cell lysis provides an explanation for the observed loss of 11-oxoreductase activity [14]. It was shown that the reductase activity of 11β-HSD1 is dependent on a high $NADPH/NADP^+$ ratio [21]. Importantly, the demonstration of a physical interaction between H6PDH and 11β-HSD1 suggested a coupling of 11β-HSD1 activity and the metabolic state of the cell [22,23]. In most organs, 11β-HSD1 is coexpressed with H6PDH [24]. Thus, 11β-HSD1 functions *in vivo* predominantly as a reductase and its activity is dependent on the availability of hexose-6-phosphates and NADPH.

2. Glucocorticoids as substrates of 11β-HSD1

Initially, 11β-HSD1 has been identified in a search for the enzyme interconverting cortisol and cortisone [8]; hence, the first substrates identified for this enzyme were glucocorticoids (cortisone and cortisol in humans, 11-dehydrocorticosterone and corticosterone in rodents). As mentioned above in most organs and cell types analyzed so far, 11β-HSD1 is coexpressed with H6PDH and it therefore has an important role in the regeneration of active glucocorticoids and in the prolongation of their biological half-life. The highly efficient hepatic conversion to their potent 11β-hydroxylated forms explains the therapeutic effect of the endogenous 11-oxoglucocorticoid cortisone and the synthetic prednisone. The tissue-specific interconversion of glucocorticoids by 11β-HSD1 and 11β-HSD2 allows a fine-tuned regulation of the threshold concentrations of glucocorticoids that are required to exert a biological effect in a given cell type and tissue. Interestingly, the synthetic glucocorticoids bearing a fluoride atom at position 9 of the steroid backbone like dexamethasone, betamethasone, 9α-fluorocortisol and triamcinolone as well as the androgen fluoxymesterone are barely metabolized by 11β-HSD2 *in vitro* and the ratio of 11β-hydroxyl to 11-oxo derivative is far on the side of the active 11β-hydroxyl form ([25–28] and own unpublished observations). Thus, these synthetic glucocorticoids circumvent the tissue-specific modulation of the endogenous glucocorticoids and of synthetic non-fluorinated forms such as prednisone/prednisolone that generally have less severe adverse effects than the fluorinated derivatives upon prolonged systemic administration.

The production of the active endogenous 11β-hydroxyglucocorticoids is tightly controlled by the hypothalamus–pituitary–adrenal axis. In humans, over 95% of circulating cortisol is bound to cortisol-binding globulin; thus, only a small fraction is unbound and physiologically available. The inactive form cortisone is approximately 50% protein-bound and a higher fraction is available to peripheral target cells expressing 11β-HSD1. The active glucocorticoids generated by 11β-HSD1 then enhance the local GR-dependent effects on gene expression. Understanding the relative contribution of the fraction of the active glucocorticoids formed by 11β-HSD1 compared with that released from the adrenals clearly needs further research.

An over production of glucocorticoids due to adrenal tumors or administration of high doses of glucocorticoids for a prolonged period of time during therapy can cause Cushing's disease, with metabolic disturbances resembling those observed in patients with metabolic syndrome [29]. Since circulating glucocorticoid levels are not elevated in patients with metabolic syndrome, it was postulated that an elevated local regeneration of active glucocorticoids by 11β-HSD1 may be an important factor in the development of complications associated with the metabolic syndrome [30,31]. Therefore, a number of transgenic mouse models with altered expression of 11β-HSD1 have been developed and were investigated for changes in metabolic functions [32,33].

Early studies on global 11β-HSD1 knock-out mice were very promising, with data showing an improved insulin sensitivity and plasma lipid profile [34]. The 11β-HSD1-null mice, developed on an obesity-resistant MF1 background, displayed reduced activation of the major gluconeogenic enzymes glucose-6-phosphatase and phosphoenolpyruvate carboxykinase upon fasting, possibly due to decreased intrahepatic corticosterone levels, and they resisted hyperglycemia upon high-fat diet. The same mice were reported to have increased insulin sensitivity, lower circulating triglycerides, possibly due to increased fat catabolism, and increased plasma levels of anti-atherogenic HDL cholesterol [35]. To further establish the role of 11β-HSD1 in obesity-related complications, MF1-based *HSD11B1*$^{-/-}$ mice were backcrossed to an obesity prone C57BL/6J background. Similarly, these mice exhibited an improved glucose tolerance and insulin sensitivity as well as a favorable lipid profile on a high-fat and high-cholesterol diet [36]. These observations were contrasted by a recent study by Harno et al. who constructed a global *HSD11B1* knock-out mouse strain on a C57BL/6J background [37]. Surprisingly, these mice did