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11β-Hydroxysteroid Dehydrogenase Enzymes Modulate Effects of Glucocorticoids in Rheumatoid Arthritis Synovial Cells

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Abstract
The tissue availability of active glucocorticoids (cortisol in humans) depends on their rate of synthesis from cholesterol, downstream metabolism, excretion and interconversion. The latter is mediated by the 11β-hydroxysteroid dehydrogenases (11βHSDs). In this review, we summarize the features of the two isoenzymes, 11βHSD1 and 11βHSD2, and current available experimental data related to 11βHSDs, which are relevant in the context of synovial cells in rheumatoid arthritis (RA). We conclude that due to complex feedback mechanisms inherent to the hypothalamic-pituitary-adrenal axis, currently available transgenic animal models cannot display the full potential otherwise inherent to the techniques. Studies with tissue explants, mixed synovial cell preparations, cell lines derived from synovial cells, and related primary cells or established cell lines indicate that there are relatively clear differences between the two isoenzymes. 11βHSD1 is expressed primarily in fibroblasts and osteoblasts, and may be responsible for fibroblast survival and aid in the resolution of inflammation, but it is also involved in bone damage. 11βHSD2 is expressed primarily in macrophages and lymphocytes, and may be responsible for their survival, suggesting that it is critical in chronic inflammation. The situation in synovial tissue would allow 11βHSD2-expressing cells to tap the energy resources of 11βHSD1-expressing cells. The overall properties of this local glucocorticoid interconversion system might limit therapeutic use of glucocorticoids in RA.

Introduction

The sheer number of papers (almost 8,000), which can be found in a PubMed search using the search string '(glucocorticoid OR cortisone OR cortisol OR prednisone OR prednisolone OR dexamethasone) AND rheumatoid arthritis', indicate that the introduction of glucocorticoids into the treatment of rheumatoid arthritis (RA) by Hench et al. [1] must be considered a success. In the late 1960s, a role for peripheral cortisone-cortisol interconversion in RA was described [2] and involvement of synovial tissue in this interconversion was shown [3]. However, more detailed elucidation of the underlying mechanisms was possible only after the necessary techniques became available [4].

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11β-Hydroxysteroid Dehydrogenases

The principle biochemical pathways involved in glucocorticoid synthesis from cholesterol, their interconversion, their downstream metabolism and their excretion are known (fig. 1) and have been described in excellent reviews [5, 6]. It is now evident that the effects of the endogenous glucocorticoids, as well as therapeutic drugs, depend critically on the intra-tissue activities of the enzymes involved in their interconversion, the 11β-hydroxysteroid dehydrogenases (11βHSDs) [7].

In humans, there exist two 11βHSD isoenzymes (EC 1.1.1.146), which are encoded by separate genes and catalyze remarkably different reactions. The type 1 enzyme (11βHSD1) is encoded by the gene HSD11B1 and predominantly mediates the conversion of 11-oxosteroids to their corresponding 11β-hydroxysteroids using NADPH as a cofactor, but might work in a reverse mode under certain circumstances [8, 9]. By contrast, the type 2 enzyme (11βHSD2) is encoded by the gene HSD11B2 and exclusively mediates the conversion of 11β-hydroxysteroids to their corresponding 11-oxosteroids using NAD^+ as a cofactor [10, 11].

Although their most prominent physiological roles are the reactivation of cortisone into the glucocorticoid receptor (GR) agonist cortisol (11βHSD1) and the inactivation of cortisol into the biologically inactive cortisone (11βHSD2), both enzymes can metabolize various additional substrates with similar structures. Generally, these additional substrates are not prominent, but in principle all steroidal substances containing 11-keto/11-hydroxy functional groups can compete with the endogenous corticosteroids for the catalytically active sites of the 11βHSDs [12]. Among these are prednisone or prednisolone, as well as some 7-keto/7-hydroxy cholesterol metabolites, which are sterically similar to normal 11βHSD substrates [9, 13]. Moreover, these metabolites can compete with glucocorticoids for the 11βHSDs active sites [14], which may result in alterations of net conversion rates of cortisol and cortisone, respectively, strongly depending on the concentrations of alternative substrates within a given tissue.

In line with their opposing catalytic activities, expression of both 11βHSD isoenzymes seems to follow simple rules. 11βHSD1 expression levels are highest in tissues where the GR signaling is important, e.g. in the liver [7, 8]. In contrast, 11βHSD2 expression is strong in tissues in which either GR activation should be avoided or glucocorticoids would interfere with specific mineralocorticoid signaling, e.g. in the kidney [7, 10, 11, 15]. This dual function of 11βHSD2 was shown in detail in a study in human fetal tissues by Condon et al. [16]. In addition, overexpression of 11βHSD2 in pituitary tumors was shown to be at least in part responsible for cell proliferation [17].

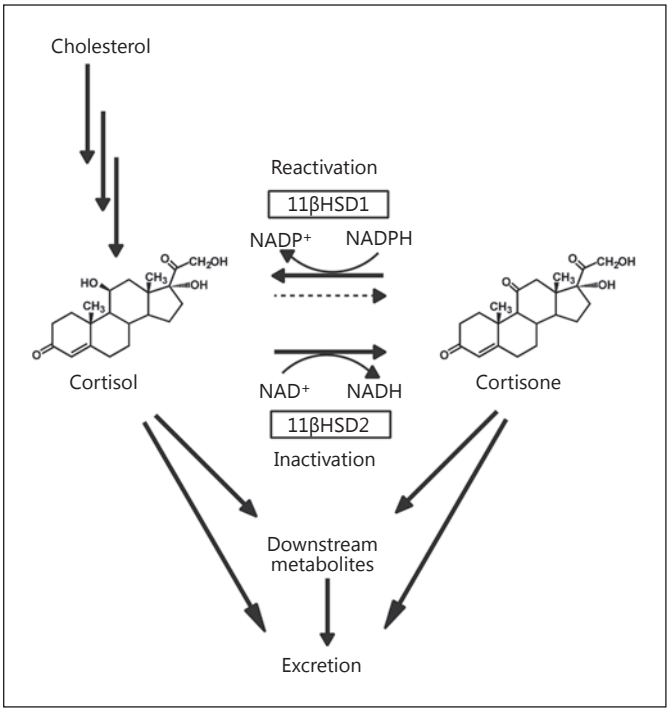

Fig. 1. Pathways involved in glucocorticoid metabolism. Glucocorticoid synthesis from cholesterol, downstream metabolism and excretion are summarized by arrows. The reactions catalyzed by the two 11βHSD isoforms are shown. The dashed arrow indicates the backward reaction seen only for purified 11βHSD1 in vitro.

Lessons Learned and Not (Yet) Learned from Animal Models

Transgenic animal models can yield valuable information to elucidate the roles of individual genes or proteins. Accordingly, available mice with targeted inactivation (knock-out) of 11βHSDs were soon analyzed for phenotypic alterations related to inflammatory diseases [reviewed in 18]: mice without 11βHSD1 exhibit a complex but subtle inflammatory phenotype. More recently, it was shown that lack of 11βHSD1 exaggerates inflammation in various mouse models of experimental arthritis [19]. In a rat arthritis model, inhibition of local glucocorticoid reactivation by 11βHSD1, as well as inhibition of GR signaling by RU486, increased inflammatory paw volume (as

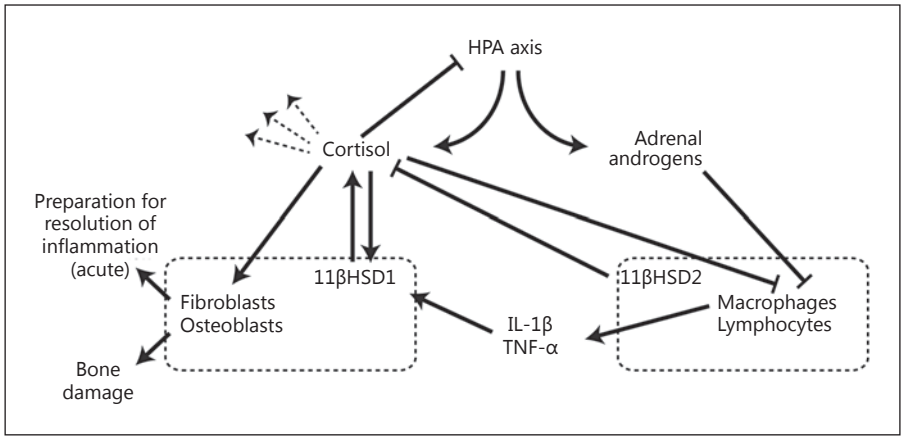

Fig. 2. 11βHSDs modulate the amount of cortisol and its effects. The amount of cortisol (the active glucocorticoid) depends on the functional HPA axis and the activities of the two 11βHSD isoenzymes: 11βHSD1 increases cortisol and 11βHSD2 reduces cortisol; too much cortisol inhibits the HPA axis and reduces the anti-inflammatory androgens. This becomes critical in cells not responding to cortisol because of 11βHSD2 expression. Arrows indicate synthesis, induction or activation; blunted lines indicate degradation or inhibition.

readout for inflammation) [20]. But generally the phenotypes seen in these experiments are associated with adrenal hyperplasia and elevated systemic corticosterone levels (the active glucocorticoid in rodents), which seem to compensate for the absence of local reactivation of glucocorticoids by 11βHSD1.

This is mirrored in humans, in whom reduced 11βHSD1 activity caused by various genetic defects leading to lower locally available concentrations of cortisol (with or without significant changes of cortisol concentrations in the circulation) alter the hypothalamic-pituitary-adrenal (HPA) axis towards hyperandrogenism [6, 21]. This implies that presumably all experimental approaches using systemic manipulation of 11βHSD1 activity (both, transgenic and pharmacological) may trigger interfering systemic responses, i.e. dysregulation of the HPA axis and alterations of the ratio of glucocorticoids versus adrenal androgens (fig. 2). Adrenal androgens themselves and their metabolites are important modulators of inflammation in RA, as reviewed previously [22].

From transgenic animal studies, much less evidence exists concerning the role of 11βHSD2 in arthritis. No clear effects were seen in the initial studies [18]. More recently, transgenic overexpression of 11βHSD2 in osteoblasts was used to reduce the local glucocorticoid signaling. Indeed, it inhibited bone loss in the inflammatory model of K/BxN mouse serum-induced arthritis that usually leads to bone resorption, as demonstrated in the wild-type controls [23]. Moreover, this cell type-restricted alteration of glucocorticoid interconversion reduced local inflammatory activity, most likely via changes in the local levels of pro- and/or anti-inflammatory cytokines.

Taken together, notwithstanding the conclusiveness transgenic animal approaches can provide, results with these models alone cannot at present clarify the exact roles of the two 11βHSDs in arthritis synovial cells. There obviously is a need for more mouse models with cell type-specific knock-out (or overexpression) of 11βHSDs to delineate clearly the effects of each isoenzyme on glucocorticoid signaling in individual cell types and the systemic implications thereof – via paracrine or (neuro)endocrine (feedback) mechanisms [21, 24].

Studies Involving Synovial Cells and Related Specific Cell Types

In recent years, a solid body of evidence from more 'classical' experimental approaches appeared for the elucidation of 11βHSD-mediated modulation of glucocorticoid signaling in synovial cells. Three types of cell preparations are used in most of the functional studies mentioned: (1) tissue explants, homogenates or freshly isolated mixed synovial cells – which may best represent the in vivo mRNA expression, enzyme activities or metabolite concentrations, but lack resolution as to the cell types responsible; (2) cells propagated in vitro from synovial cell preparations – mostly synovial fibroblasts, which can be expanded and cultured for a long time, or (3) cell types that are found in RA synovial tissue but are more easily accessible from other sources, e.g. from blood or bone, etc.

As with the animal studies, more knowledge has accumulated concerning the function of 11βHSD1 than 11βHSD2. Cooper et al. [25] found in an osteosarcoma cell line and in primary osteoblasts that interleukin (IL)-1β or tumor necrosis factor (TNF)-α induced 11βHSD1 gene expression and activity, which increased glucocorticoid sensitivity of the cells. Expression of 11βHSD1 in tissue sec-

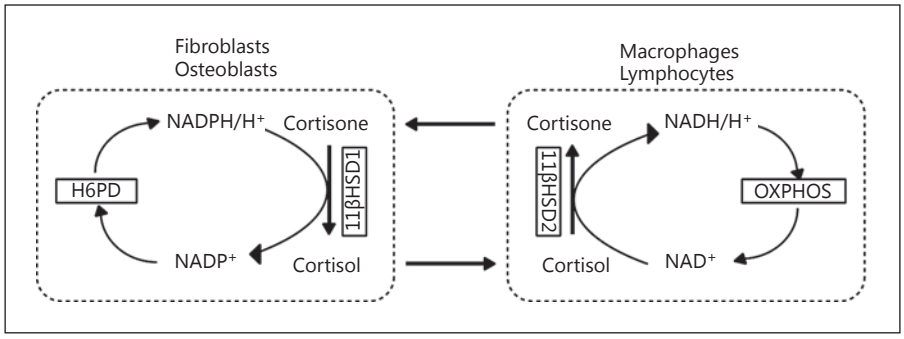

Fig. 3. Energy transfer by synovial glucocorticoid metabolism. 11βHSD2-expressing cells can generate $NADH/H^+$ from oxidation of cortisol, which can be further used in oxidative phosphorylation (OXPHOS) to provide ATP. Glucocorticoids are the diffusible intermediates. 11βHSD1 regenerates cortisol using $NADPH/H^+$, which is generated by the essential enzyme hexose-6-phosphate dehydrogenase (H6PD).

tions from patients with osteoarthritis (OA) and RA was found in the lining and sublining area by immunohistochemistry, and 11βHSD1 expression co-localized with the macrophage marker CD163 in double immunofluorescence [26]. Indeed, 11βHSD1 is induced in human monocytes upon differentiation to macrophages [27]. 11βHSD1 expression was induced by the anti-inflammatory IL-10 in synovial macrophages from control patients, but not in macrophages from RA patients [28]. In addition, CD163– cells, typically activated macrophages, but not CD3+ lymphocytes or prolyl 4-hydroxylase-positive fibroblasts, expressed 11βHSD1 [26]. However, the enzyme is also expressed in CD90+ fibroblasts from OA and RA patients [29], which might suggest that there are two subpopulations of synovial fibroblasts. In this study, IL-1β or TNF-α induced expression of 11βHSD1 and re-activation of cortisone by 11βHSD1 inhibited IL-6 production. Glucocorticoids also induce expression of 11βHSD1 and act synergistically with IL-1β or TNF-α in synovial fibroblasts and osteoblasts [30]. Cytokine-mediated induction of 11βHSD1 involves NF-κB signaling [31] and is necessary for secretion of a Wnt-antagonist by synovial fibroblasts [32].

Together with the cytokine signaling inhibitor studies in rats [20] and the knock-out mice work [19], a picture emerges in which initiation of inflammation by IL-1β/TNF-α prepares (sensitizes) synovial fibroblasts via expression of 11βHSD1 for the anti-inflammatory activity of glucocorticoids. This should contribute to resolution of local inflammation [4].

11βHSD2 entered the field of RA quietly, as it was found to be among 9 genes (from 4,300 analyzed) that were upregulated in peripheral blood mononuclear cells from patients with recent-onset RA at least 3-fold compared to healthy individuals [33]. In synovial tissue of patients with RA and OA who underwent knee replacement surgery, we found expression of 11βHSD2 in CD163+ macrophages and CD163– cells by double immunofluorescence labelling [26]. In this study, the ratio of cells positive for 11βHSD2 versus cells positive for 11βHSD1 was higher in RA than in OA, and biochemical analysis had shown that in RA the reactivation of cortisone to cortisol is impaired.

A subsequent study using samples from various anatomical sites indicated 11βHSD2 expression in synovial macrophages but a net reduction of cortisone [34]. An additional cell type of interest was found to express 11βHSD2: in lymphoblastoid B cell lines from RA-discordant twins, 11βHSD2 was the second most overexpressed gene in RA cases. Protein expression in synovial tissue of patients was correlated significantly with an inflammation score, suggesting a link between expression of 11βHSD2 and the degree of inflammation [35]. Interestingly, a similar link was also found for 11βHSD1 activity and levels of erythrocyte sedimentation rate [34].

The Inflamed Synovium – A Place for Two 11βHSDs

Thus, both 11βHSDs seem to be upregulated in RA (and possibly even in OA, when compared to non-inflamed tissue), albeit in different cell types. 11βHSD1 is most prominent in fibroblasts and osteoblasts, whereas 11βHSD2 is more prominent in macrophages and B cells (fig. 2). 11βHSD2 is not found in mouse macrophages during acute inflammation [36]. It is not expressed during differentiation of isolated human monocytes to macrophages, but it is found in the THP-1 macrophage cell line [27], consistent with the finding of an association of 11βHSD2 with cell proliferation [17]. In addition, 11βHSD2 expression was downregulated in osteoblasts upon treatment with IL-1β or TNF-α [25]. In combination, available experimental data suggest that 11βHSD2 is expressed: (1) in chronic inflammation, (2) in cells from the leukocyte lineage and (3) in cells that presumably seek to avoid glucocorticoid-induced apoptosis (fig. 2). The

last appears to be quite reasonable, as glucocorticoids induce apoptosis in monocytes and macrophages, etc., but prevent apoptosis in other cells, such as fibroblasts [37].

However, there might be another pathway by which 11βHSD2 and glucocorticoids could provide an advantage to a cell surrounded by a growing fibroblast population: 11βHSD2 would allow a cell to tap the biosynthetic/energy resources of adjacent cells based on the shuttling of the diffusible glucocorticoids. Fibroblasts (or osteoblasts) reduce cortisone to cortisol, a reaction driven by their fuels. On the other side, a cortisol-avoiding macrophage or lymphocyte will inactivate cortisol in order to avoid apoptosis and gain some additional $NADH/H^+$, which can be further used in oxidative phosphorylation to provide ATP (fig. 3). That would provide a small but almost effortless energy income for macrophages/lymphocytes at the expense of fibroblasts.

Conclusions

The characteristics of the 11βHSDs explain the tightrope walk of glucocorticoid therapy for RA and, possibly, other chronic inflammatory diseases. Inhibition of 11βHSD1 may protect bone at the price of hindering resolution of inflammation. Inhibition of 11βHSD2 is accompanied by mineralocorticoid-like side effects, as does application of glucocorticoids in high doses. However, dosage should be high enough to hit the sensitive cells (and/or started before the 11βHSD2 even starts working in the synovial tissue). Combination therapies with biologicals (anti-IL-1β or anti-TNF) should reduce the side effects on bone. Either a targeted delivery system or a tool for cell type-specific inhibition of 11βHSD2 expression seems necessary to affect macrophages and lymphocytes optimally.

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