

# Arthritis and endogenous glucocorticoids: the emerging role of the 11 $\beta$ -HSD enzymes

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It is somewhat in contrast to the great importance of *synthetic* glucocorticoids in the systemic and intra-articular treatment of rheumatoid arthritis (RA) and other inflammatory rheumatic diseases<sup>1-3</sup> that we do not know whether *endogenous* glucocorticoid action contributes to the susceptibility and/or severity of RA. In this issue of the journal, Hardy and colleagues describe an interesting study into the local and systemic metabolism of endogenous glucocorticoids in inflammatory arthritis (*see page 1204*).<sup>4</sup> Their findings demonstrate the existence of substantial glucocorticoid metabolism in the joint. Thus, the synovial tissue is reported to predominantly activate glucocorticoids through the action of 11 $\beta$ -hydroxysteroid dehydrogenase type 1 (11 $\beta$ -HSD1). In patients with RA, the activity of this enzyme was found to correlate positively with donor erythrocyte sedimentation rate (ESR). Interestingly, 11 $\beta$ -HSD1 expression was primarily seen in fibroblasts. However, synovial tissue seems also able to convert active cortisol back to inactive cortisone. This pathway is driven by synovial macrophages expressing a glucocorticoid-inactivating enzyme, 11 $\beta$ -hydroxysteroid dehydrogenase type 2 (11 $\beta$ -HSD2). In order to better understand these findings, we should first like to give a short overview of how endogenous glucocorticoids are regulated and metabolised on a cellular level, and the roles of 11 $\beta$ -HSD enzymes in the latter process.

## CELLULAR METABOLISM OF ENDOGENOUS GLUCOCORTICOIDS

Endogenous glucocorticoids are regulated via the hypothalamic-pituitary-adrenal

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axis and control electrolyte and fluid homeostasis, fuel metabolism and immune and stress responses.<sup>5-10</sup> Cortisol acts primarily through activation of the cognate intracellular glucocorticoid receptor at the target tissues. However, cytokines, growth factors and specific enzymes modulate this control at a local level.<sup>11 12</sup>

For a long time, it was thought that glucocorticoid actions on target tissues were determined by glucocorticoid plasma concentrations and the tissue-specific density glucocorticoid receptors only. However, over the years it has become apparent that the 11 $\beta$ -HSDs are key regulators of glucocorticoid pre-receptor metabolism. By changing the balance between active and inactive glucocorticoids within the cell, these enzymes are able to govern the access of glucocorticoids to their cognate receptors in many tissues.<sup>13-15</sup>

## FUNCTIONS AND TISSUE DISTRIBUTION OF 11 $\beta$ -HSD ENZYMES

11 $\beta$ -HSD1 facilitates the regeneration of biologically active cortisol and corticosterone from their inactive forms—namely, cortisone and 11-dehydrocorticosterone, by its oxidoreductase (11 $\beta$  reductase) action.<sup>16</sup> Through 11- $\beta$  dehydrogenation, the same enzyme can effect the reverse reaction, thereby facilitating the inactivation of cortisol to cortisone.<sup>17</sup> In contrast, 11 $\beta$ -HSD2 has dehydrogenase activity only—that is, it *unidirectionally* catalyses the conversion of active glucocorticoids to their inactive metabolites (fig 1A). The balance between 11 $\beta$ -HSD type 1 and type 2 appears to modulate intracellular glucocorticoid concentrations and sensitivity. Shifts in this balance have been associated with marked phenotypic and functional cell changes.<sup>10</sup> Furthermore, cytokines such as interleukin (IL)1 $\beta$  and tumour necrosis factor  $\alpha$  (TNF $\alpha$ ) inhibit 11 $\beta$ -HSD2 while potentially stimulating 11 $\beta$ -HSD1 activity.<sup>18 19</sup> This increase in 11 $\beta$ -HSD1 activity increases the amount of intracellularly available active glucocorticoids, which counteracts the inflammatory process by

inhibiting cell proliferation and inducing cell differentiation (fig 1B).<sup>10 19</sup>

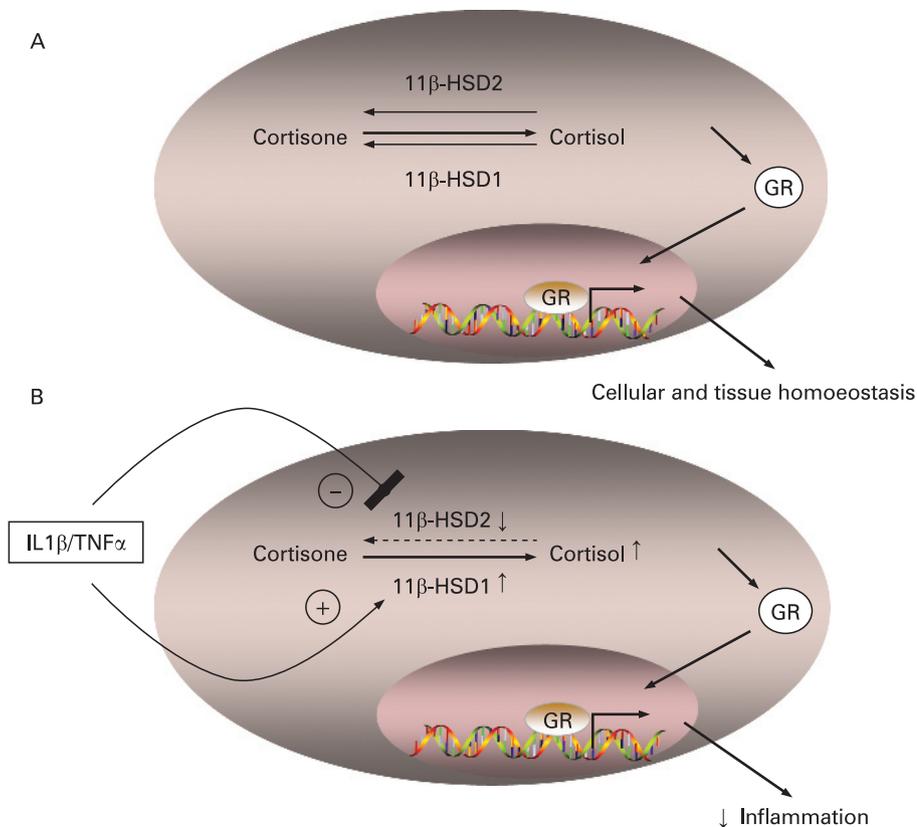
## 11 $\beta$ -HSD ENZYMES AND BONE

Steroid hormone-modifying enzymes are currently gaining prominence as pre-receptor regulators of steroid hormone action *in vivo*. Both 11 $\beta$ -HSD type 1 and 2 have been shown to occur in bone cells where they seem to act as “autocrine” regulators of cell function by augmenting or reducing local glucocorticoid concentrations and sensitivity. These mechanisms are not only likely to be of physiological relevance in the differentiation of bone cells,<sup>20</sup> but may contribute to the deleterious effects of glucocorticoids on bone in circumstances such as ageing or inflammation.

While the expression of 11 $\beta$ -HSD2 mRNA in human bone is strong during fetal development but later declines,<sup>21 22</sup> recent studies by Stewart and colleagues show that, in humans, the activity of osteoblastic 11 $\beta$ -HSD1 increases with age and glucocorticoid exposure.<sup>23</sup> Interestingly, osteosarcoma cell lines of both human (eg, MG-63) and rodent origin show 11 $\beta$ -HSD2 mRNA expression and enzymatic activity, suggesting that 11 $\beta$ -HSD2 expression may be switched on in pathological situations.<sup>24 25</sup> In MG-63 cells, inflammatory cytokines such as IL1 $\beta$  and TNF $\alpha$  have been shown to dose-dependently inhibit 11 $\beta$ -HSD2 activity while potentially stimulating 11 $\beta$ -HSD1 activity.<sup>18 19</sup> Such actions would result in increased amount of active hormone within the cell and it is these data in particular that suggest a role for the 11 $\beta$ -HSD enzymes in inflammation-mediated changes of local glucocorticoid metabolism. In fact, these mechanisms may play a role in the pathogenesis of inflammation-mediated bone loss.

## ROLE OF ENDOGENOUS GLUCOCORTICOIDS AND 11 $\beta$ -HSD ENZYMES IN ARTHRITIS

So far, we have focused on bone and bone cells. However, in order to shed some light on the role of endogenous glucocorticoid action and the importance of 11 $\beta$ -HSD enzymes in arthritis, other cells such as synoviocytes and fibroblasts need to be considered. Unfortunately, knowledge in this area is very limited and the work by Hardy and colleagues provides new insights that may allow us to better understand the role of endogenous glucocorticoids in arthritis.



**Figure 1** (A) Local metabolism of endogenous glucocorticoids. (B) Local metabolism of glucocorticoids in inflammation. GR, glucocorticoid receptor; 11β-HSD, 11β-hydroxysteroid dehydrogenase; IL1β, interleukin 1β; TNFα, tumour necrosis factor α.

There are some observations which underline the need for intensive research in this area. First, in humans, administration of metyrapone to reduce endogenous glucocorticoid production increases disease activity in RA.<sup>26</sup> Second, in mixed synovial cells from patients with RA, a reduced capacity for local reactivation of cortisone to cortisol has been recently demonstrated.<sup>27</sup> Third, using a rodent model of immune inflammation we have recently found that the overexpression of 11β-HSD2 attenuates inflammatory activity, thus pointing to a role of glucocorticoid-modulating enzymes and local glucocorticoid levels in the inflammatory process (Buttgereit, Seibel and Zhou, unpublished observations). These experimental results appear to contradict some of the in vitro and human (clinical) data and the results that should be expected from the mechanisms depicted in fig 1: On the one hand, inhibition of endogenous glucocorticoids increases the activity of the arthritic process, whereas on the other, facilitated inactivation of endogenous glucocorticoids via overexpressing 11β-HSD2 yields the opposite effect—that is, attenuates arthritis. This example demonstrates that we have not understood yet to what extent

endogenous glucocorticoids contribute to initiation and perpetuation of the arthritic process, especially in RA.

Over the past years, the groups headed by Mark Cooper and Jonathan Seckl have been successful in advancing this interesting field of research.<sup>28–31</sup> First, they showed that synovial fibroblasts express 11β-HSD1 in vitro and in vivo.<sup>29</sup> Second, their results indicate that in synovial cells (and in osteoblasts) 11β-HSD1 activity is up-regulated by proinflammatory cytokines.<sup>29–30</sup> From these data the authors have derived the hypothesis that 11β-HSD1 might generate high levels of glucocorticoids within the inflamed joint and that this might contribute to peri-articular osteoporosis. The current study extends these findings significantly. The authors demonstrate that (a) 11β-HSD1 is functionally active in synovial tissue samples from patients with RA—that is, synthesises active cortisol from inactive cortisone and (b) there is a positive correlation for glucocorticoid activation in the synovium with preoperative ESR (but not with C-reactive protein (CRP) levels). The latter observation further emphasises that the metabolism of endogenous glucocorticoids is among the determinants which have influence on

the activity/severity of the arthritic process. This assumption is corroborated by the finding that IL6 production in synovial-derived fibroblasts from patients with RA is significantly reduced in the presence of 100 nmol/l cortisone.<sup>29</sup> This could be prevented by co-treatment with an 11β-HSD inhibitor, which emphasises the potential for autocrine activation of glucocorticoids in synovial fibroblasts.<sup>29</sup> This ultimately leads to the question: Does it make sense to target therapeutically the 11β-HSD metabolism for the treatment of arthritis?

### THERAPEUTIC TARGETING OF 11β-HSD METABOLISM TO TREAT ARTHRITIC CONDITIONS

Several different approaches have been made and are being made to improve the benefit–risk ratio of glucocorticoid treatment.<sup>32</sup> In this regard, the investigation of glycyrrhetic acid as a potential drug needs to be mentioned here. Furthermore, BX-1—a small molecule inhibitor of 11β-HSD—has been developed.<sup>33</sup> This substance is the pharmacologically active metabolite of a prodrug contained in the liquorice root *Glycyrrhiza glabra*. In animal models or RA, BX-1 reduced inflammation and tissue destruction as well as bone erosion by locally increasing cortisol concentrations in affected tissues.<sup>33</sup> This illustrates the potential impact of understanding better the endogenous glucocorticoid metabolism: Successful local targeting of the inflammatory process such as arthritis would prevent systemic undesired effects of anti-inflammatory treatment with exogenous glucocorticoids.

**Competing interests:** None.

*Ann Rheum Dis* 2008;**67**:1201–1203.  
doi:10.1136/ard.2008.092502

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