THEMATIC REVIEW

Recycling glucocorticoids: therapeutic implications of the 11β-HSD1 enzyme system

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Abstract

Endogenous glucocorticoids and commonly used oral glucocorticoids have the property of existing in an inactive and active form in vivo. The inactive form can be converted back to the active form, or ‘recycled’ in cells and tissues that express the 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) enzyme. This recycling provides an important contribution to the action of glucocorticoids. This review examines the literature relating to the importance of 11β-HSD1 activity during glucocorticoid treatment, with an emphasis on studies examining bone and joint disease and the ability of glucocorticoids to suppress inflammatory damage in models of arthritis. Animal models with global or selective deletion of 11β-HSD1 have determined the extent to which this recycling is important in normal physiology and during treatment with oral glucocorticoids. These studies demonstrate that 11β-HSD1-mediated recycling of inactive glucocorticoids has a substantial action and indeed is responsible for the majority of the effects of orally administered glucocorticoids on a range of tissues. Importantly, the anti-inflammatory actions of glucocorticoids appear largely through this mechanism such that mice that lack 11β-HSD1 are resistant to the anti-inflammatory actions of glucocorticoids. The recognition that to a large extent the circulating inactive counterpart of these glucocorticoids is more important to anti-inflammatory effects than the active glucocorticoid presents novel opportunities to more selectively target glucocorticoids to tissues or to reduce the likely side effects.

Introduction

Despite the introduction of a range of biological therapies aimed at specific aspects of the immune response, glucocorticoids are still widely used for their broad and potent therapeutic effects. Despite considerable efforts in trying to develop novel and more clinically effective glucocorticoids, the types of glucocorticoids used today have not changed substantially over many decades (Hardy et al. 2020). Prednisone and prednisolone continue to be the most utilised oral glucocorticoids clinically. These are structurally very similar to the endogenous glucocorticoids found in humans, cortisone and cortisol (referred to as hydrocortisone when used as a pharmaceutical) and those in rodents, dehydrocorticosterone (DHC) and corticosterone. These glucocorticoids have the interesting property that they can change from being entirely inactive at the glucocorticoid

Key Words

- glucocorticoid
- steroid dehydrogenases
- bone formation and resorption
- inflammatory diseases
- corticosteroids
receptor (GR) to powerful agonists just by a modification of the chemical group at the 11 position of the steroid ring. Thus prednisone, cortisone and DHC are inactive and require modification at the 11beta position to have glucocorticoid action (Fig. 1). The intracellular enzymes that mediate this modification are the 11beta-hydroxysteroid dehydrogenases (11beta-HSDs). Although three 11beta-HSD enzymes have been identified across species, two are thought to mediate reactions in humans and rodents. The type 1 enzyme is bidirectional but appears to primarily be an activator of glucocorticoids from their inactive forms (mediating the reductase reaction). The ability to catalyse the reductase reaction is maintained by the coexpression of the H6PDH enzyme which generates NADPH, the cofactor required for 11beta-HSD1 reductase activity. The type 2 enzyme is considered to be a purely inactivating enzyme for the glucocorticoids discussed above and has an important role in inactivating glucocorticoids within the renal distal convoluted tubule cells thus preventing these glucocorticoids from binding the MR for which they would have a similar affinity to that of aldosterone. Although the two 11beta-HSD enzymes can be thought of independently and indeed are evolutionary distinct in their origins, the two enzymes interact through the provision of enzyme substrates for the other enzyme. Since the human adrenal gland predominantly secretes cortisol with only small amounts of cortisone the 11beta-HSD2 enzyme (primarily in the kidney) is the source of the cortisone utilised by 11beta-HSD1. Thus the cortisone used in reactions by 11beta-HSD1 is ‘recycled’ back to cortisol. Orally administered prednisone has almost complete conversion to prednisolone on first-pass metabolism in the liver (Uribe et al. 1982) which is why prednisone and prednisolone are often referred to interchangeably in the medical literature. For oral prednisone to have effects mediated by 11beta-HSD1 outside of the liver this drug again needs to be converted back to prednisone in tissues expressing 11beta-HSD2 before it can be a substrate for 11beta-HSD1 mediated conversion back to (recycling) prednisolone within target cells (Fig. 2).

Glucocorticoids that can exist in two forms (active and inactive) in vivo have the potential to be used differentially in a cell-specific and context-dependent manner. Although the active form would be capable of having direct effects in all cells and tissues (assuming the cells do not express inactivating enzymes such as 11beta-HSD2) cells that express the 11beta-HSD1 enzyme would be exposed to both the direct effects of active glucocorticoids and the additional impact of intracellularly generated active steroid from the inactive precursor form. Evidence suggests that the expression of 11beta-HSD1 is indeed cell-specific but also subject to dramatic changes in expression level. Examples of tissues/cell types that express 11beta-HSD1 at a significant level include liver and adipose tissue, various cells within skin, osteoblasts (bone-forming cells), fibroblast-like synovial (FLS) cells and various types of immune cell (most prominently macrophages) (Chapman et al. 2013, Gathercole et al. 2013). Although many factors have been reported to regulate the expression level of 11beta-HSD1, including differentiation status, age and growth hormones/insulin-like growth factor 1 the most dramatic increases in expression level are seen in various cell types in response to inflammation (Chapman et al. 2013). The tissue-specific increase in 11beta-HSD1 expression and enzyme activity in response to inflammation has particular relevance to the use of glucocorticoids as a treatment of inflammatory disease (Hardy et al. 2013). In this situation, glucocorticoids that are substrates for 11beta-HSD1 are likely to accumulate in an active form, and have greater tissue action, at sites of inflammation and specifically in the cells with high inflammation induction of 11beta-HSD1. This selective recycling in these tissues could lead to positive effects if there was a useful anti-inflammatory action of these steroids but could also cause greater side effects if the cells expressing 11beta-HSD1 are detrimentally impacted by high glucocorticoid exposure. These issues have been most studied in the context of the role of 11beta-HSD1 in inflammatory joint conditions such as rheumatoid arthritis where the synovial tissue of the inflamed joint expresses high levels of glucocorticoids, an effect which is likely to be even further amplified during treatment with oral glucocorticoids (Schmidt et al. 2005, Hardy et al. 2008).

![Figure 1](https://joe.bioscientifica.com) Interconversion of endogenous and commonly used synthetic glucocorticoids by the 11beta-HSD enzymes. Enzyme reactions and kinetics are very similar for each of these glucocorticoid pairs. DHC, dehydrocorticosterone.
Much of the effect of glucocorticoids in normal physiology and during treatment with glucocorticoids is likely to depend on the relative amount of action from the direct circulating glucocorticoid compared to the amount of glucocorticoid action arising from the local reactivation of glucocorticoids by $11\beta$-HSD1. In recent years access, to rodent models with global or tissue-specific deletion of $11\beta$-HSD1, the availability of pharmacological inhibitors of the $11\beta$-HSD1 enzyme and techniques to accurately measure $11\beta$-HSD1 activity in situ (Cobice et al. 2018) has allowed the amount and degree of recycling in vivo to be determined. This review describes the importance of glucocorticoid recycling in bone metabolism and in relation to inflammatory diseases affecting bone and joints and in the treatment of inflammatory diseases with glucocorticoids. We then discuss studies where recycling appears to be less important including treatment with glucocorticoids such as dexamethasone and vamorolone which exist primarily as the active form alone yet still have glucocorticoid activity. In the experiments described below DHC/cortisone and prednisone effects have been examined along with their active counterparts, corticosterone, cortisol and prednisolone depending on the species or treatment setting used. The enzyme reaction kinetics for the $11\beta$-HSD1-mediated reactions are similar for these glucocorticoids (Diederich et al. 2002, Cooper et al. 2003), and the findings using one of these glucocorticoids are likely to be translated to the others.

**Glucocorticoid recycling in bone metabolism and bone health**

A range of bone cell types are known to express $11\beta$-HSD1 (Cooper et al. 2000, Weinstein et al. 2010). Most notably the bone-forming cells, osteoblasts, express the enzyme and are sensitive in vitro to inactive glucocorticoids such as cortisone (Cooper et al. 2000). The activity of the $11\beta$-HSD1 in human and mouse bone tissue examined ex vivo demonstrates an age-related increase in activity such that bone tissue from older individuals has a much greater capacity for glucocorticoid reactivation (Cooper et al. 2000, Weinstein et al. 2010). This has been proposed as a potential mechanism for the dramatic increase in fracture risk that occurs with ageing. Cross-sectional studies support a relationship between parameters of bone health such as bone density and bone formation markers with the circulating level of cortisone suggesting a link between glucocorticoid recycling and bone health (Cooper et al. 2005). However, mice with global deletion of $11\beta$-HSD1 do not have a major bone phenotype compared to WT counterparts (Justesen et al. 2004, Henneicke et al. 2020). Furthermore, a recent phase II study examining the impact of an $11\beta$-HSD1 inhibitor on bone markers in women with osteopenia failed to show any impact (Abbas et al. 2022). As such, even though $11\beta$-HSD1 activity is present in bone its relevance to normal physiology is unclear.

The relationship between $11\beta$-HSD1 expression and bone metabolism is likely to be stronger in the
context of glucocorticoid osteoporosis. The effects of oral glucocorticoid treatment on bone formation markers in healthy volunteers most strongly correlated with measures of 11β-HSD1 activity with high 11β-HSD1 activity associated with the greatest reductions in markers of bone formation (Cooper et al. 2003). Although this is indirect evidence, it supports a significant role for 11β-HSD1 within bone (most likely osteoblasts given their role in bone formation) in mediating the detrimental effects of glucocorticoids on the tissue. Further evidence in support of this has come from studies using mice with targeted deletion of the 11β-HSD1 gene (Hsd11b1) and thus the enzyme activity. Wildtype (WT) animals receiving corticosterone in drinking water were found to develop considerable loss of trabecular bone with reduced bone volume to tissue volume, trabecular thickness and trabecular number (all important measures of trabecular bone volume to strength) (Fenton et al. 2019). These changes were accompanied by large reductions in biochemical markers of bone formation and, at a tissue level, reduction in gene expression of osteoblast markers. These changes are similar in nature to those seen in humans exposed to systemic therapeutic glucocorticoids as described above. However, 11β-HSD1 knockout mice receiving the same corticosterone treatment were found to have almost complete protection from trabecular bone loss despite a similar exposure to active glucocorticoid (corticosterone) as WT mice. These mice also had a partial but significant protection against the effects of the glucocorticoid treatment on markers of bone formation and osteoblast activity. These results indicate that the bone loss seen in response to therapeutic glucocorticoids such as corticosterone (and thus likely the structurally similar hydrocortisone and prednisone/prednisolone) is to a great extent due to recycling of glucocorticoids via 11β-HSD1.

**Rodent models of 11β-HSD1 deletion with and without glucocorticoid excess**

Although 11β-HSD1 is proposed to be important in various disease states, animals and humans that lack effective 11β-HSD1 activity (the ability to generate active glucocorticoids from inactive forms) do not appear to have any major phenotype (particularly when studied at a relatively young age) (Morgan et al. 2022). This suggests that the ability to reactivate glucocorticoids via 11β-HSD1 is not essential for general homeostasis. Likewise, clinical trials of orally administered 11β-HSD1 inhibitors have not resulted in any major adverse effects (Abbas et al. 2022, Ajjan et al. 2022, Hardy et al. 2021) although there is a subtle activation of the HPA axis as measured by the output of adrenal androgens. The situation though is very different in terms of the responses of these mice to glucocorticoid treatment. Various approaches have been used to study glucocorticoid treatment relevant to humans in mice models. These approaches to glucocorticoid administration include daily injections of glucocorticoids, implantation of pellets and addition of glucocorticoids to drinking water. Most of the more recent studies utilise drinking water supplemented with corticosterone (the rodent endogenous glucocorticoid). This appears to be an effective, reproducible and non-invasive technique for administering glucocorticoids (Gasparini et al. 2016). Mice with global deletion of 11β-HSD1 have been used in a series of studies to determine the extent to which the effects of therapeutic glucocorticoids depend on 11β-HSD1 expression. Lavery et al. treated WT mice or mice with global deletion of 11β-HSD1 with excess glucocorticoid using supplementation of corticosterone in drinking water (Morgan et al. 2014). They found that WT mice developed typical features of glucocorticoid excess (Cushing’s syndrome), but the knockout mice were protected from various features such as glucose intolerance, hepatic steatosis, adiposity, hypertension and skin thinning. This study suggested for the first time that chemical inhibitors of 11β-HSD1 might be used to protect against the clinical features of Cushing’s syndrome in humans. The mouse models used in this study were not exposed to inflammation and thus it was impossible to determine whether 11β-HSD1 had a role in either the development and progression of inflammatory diseases or their response to treatment with glucocorticoids. This is an important consideration since in a clinical setting, the majority of people treated with glucocorticoids have an underlying inflammatory condition which is sensitive to the effects of these medications.

**Rodent models of inflammatory diseases in the context of 11β-HSD1 deletion and their response to glucocorticoids**

Outside the rare situation of Cushing’s disease and adrenal tumours, glucocorticoid exposure is normally iatrogenic as a treatment for an underlying, usually inflammatory, disease. To determine the potential
importance of the 11β-HSD1 enzyme in these clinical settings, it is thus critical to study the effects of 11β-HSD1 and glucocorticoid treatment in models of inflammatory disease. Although glucocorticoids are widely used to treat inflammatory diseases affecting almost any body system, long-term oral glucocorticoid therapy is most widely used in rheumatic diseases and rheumatoid arthritis in particular.

As described above, one of the most potent inducers of 11β-HSD1 is inflammation. This is seen in many (but not all) tissues (Gomez-Sanchez & Gomez-Sanchez 2021) and has been proposed as an important part of the inflammatory response with increased expression of 11β-HSD1 allowing the local recycling of inactive to active glucocorticoids to amplify the body’s hypothalamic–pituitary–adrenal axis response to inflammation. The importance of these local changes in expression of 11β-HSD1 has been examined in mouse models of joint inflammation (polyarthritis). The TNF-Tg model of chronic polyarthritis has been the model most extensively studied. This mouse generates human TNFα within various tissues in an age-dependent manner to create a reliable and reproducible model of chronic polyarthritis (Keffer et al. 1991). Hardy et al., examined the contribution of 11β-HSD1 to the pathology of persistent chronic inflammatory disease in this model by crossing these mice with mice with global deletion of 11β-HSD1 (Hardy et al. 2018). Global deletion of 11β-HSD1 resulted in an amplified inflammatory state in TNF-Tg mice as evidenced by dramatically increased synovitis, joint destruction due to invasion of inflammatory pannus tissue into subchondral bone, and systemic bone loss. This study demonstrated that the 11β-HSD1 enzyme had an important role in suppressing many of the deleterious features of chronic arthritis including synovitis, joint destruction and systemic bone loss presumably through the local recycling of inactive circulating glucocorticoids to their active form at a local tissue level.

Given that recycling of endogenous glucocorticoids by 11β-HSD1 has an important effect to reduce the damage associated with chronic polyarthritis, it was also possible that the well-established ability of therapeutic glucocorticoids to reduce joint damage might also be mediated by this enzyme. This question was addressed in the model of arthritis described above examining the impact that therapeutic glucocorticoids would have in protecting against joint damage and systemic bone loss (Fenton et al. 2021). Similar experiments were also carried out in the K/BxN serum-induced model of polyarthritis, a mechanistically distinct model of polyarthritis (Kollidas et al. 2011). Global deletion of 11β-HSD1 was found to result in a profound resistance to the therapeutic effects of glucocorticoids seen in WT animals. 11β-HSD1 knockout mice with either type of polyarthritis demonstrated persistent synovitis and progressive joint destruction, whereas glucocorticoids effectively protected against these features in mice with intact 11β-HSD1 activity. These studies clearly demonstrated that, in the context of these models of chronic polyarthritis, the effectiveness of orally administered active glucocorticoids depended primarily on peripheral reactivation of inactivated glucocorticoids by 11β-HSD1. Importantly, this and the other experiments described above, which involve administration of the active glucocorticoid corticosterone, demonstrate that the corticosterone administered does not directly account for the anti-inflammatory effect of the glucocorticoids. Rather, corticosterone has to undergo conversion to its inactive counterpart, DHC, via the action of 11β-HSD2, primarily in the kidney. It is the resultant DHC which acts as a substrate for the enzyme 11β-HSD1 and can be reactivated locally to corticosterone. The anti-inflammatory effectiveness of corticosterone thus depends on both the ability for the glucocorticoid to be inactivated by 11β-HSD2 and then reactivated by 11β-HSD1.

Delineation of the cell and tissue types mediating 11β-HSD1 effects on therapeutic glucocorticoid action (mesenchymal vs myeloid)

Subsequent studies using these models of chronic polyarthritis have used tissue-targeted 11β-HSD1 mice to determine the tissues in which 11β-HSD1-mediated reactivation of glucocorticoids is important for the beneficial effects of therapeutic glucocorticoids in chronic polyarthritis. These studies have largely examined the extent to which 11β-HSD1 expression in either mesenchymal or myeloid cells is most important to the beneficial effects of glucocorticoids. An important caveat of these studies using Cre approaches is that the effectiveness of gene deletion in these studies is often less than with global knockout approaches and individual studies describe appropriate control experiments relating to the effectiveness of gene deletion. Increased 11β-HSD1 expression and activity have been consistently observed in the synovial tissue of humans and mice with joint inflammation/arthritis (Hardy et al. 2008). This expression
is localised to a range of cell types including FLS cells, which make up the stromal component of the synovial tissue and leukocytes (primarily macrophages) which infiltrate the synovial tissue in large numbers during inflammation. Mice with targeted deletion of 11β-HSD1 in the mesenchymal lineage were generated by crossing floxed 

\[ Hsd11b1 \] 

mice with 

\[ Twist2-cre \] 

animals (Hardy et al. 2018). In these mice, cre recombinase activity is known to target cell populations such as FLS cells, osteoblasts and chondrocytes but not leukocytes. The resulting mice with 11β-HSD1 knockout in mesenchymal cells when crossed with TNF-Tg mice had a similar inflammatory phenotype to WT mice and not the exaggerated inflammation and joint destruction seen in the global 11β-HSD1 knockout. This indicates that the anti-inflammatory actions of endogenous glucocorticoids are not mediated via mesenchymal cells and support a likely role for 11β-HSD1 expressed within leukocyte populations.

Similar studies have been done examining the 11β-HSD1 expressing tissue types responsible for mediating the beneficial effects of therapeutic glucocorticoids in chronic polyarthritis. The results are summarised in Fig. 3. In addition to the mesenchymal targeted 11β-HSD1 mice described above, myeloid-targeted 11β-HSD1 knockout mice have been generated by crossing 

\[ Hsd11b1 \] 

floxed mice with 

\[ LysM-cre \] 

mice (Zhang et al. 2017, Fenton et al. 2021). In the absence of glucocorticoid treatment, resolution of inflammatory arthritis is impaired in these mice (Zhang et al. 2017). In the context of glucocorticoid treatment, mice with deletion of 11β-HSD1 in mesenchymal cells demonstrated a maintenance of the anti-inflammatory effect of glucocorticoids, similar to WT mice (Fenton et al. 2021). Mice with myeloid deletion of 11β-HSD1 had partial resistance to the effects of glucocorticoids but not to the extent seen in 11β-HSD1 global knockout mice. The failure of either mesenchymal or myeloid-targeted 11β-HSD1 knockout models to reproduce the full effect of global 11β-HSD1 deletion might be due to 11β-HSD1 expressed in other cell types being responsible for the anti-inflammatory actions of glucocorticoids or a more complex relationship between glucocorticoid activation and action between mesenchymal and myeloid cells. An interaction between these cell types seemed plausible given the very close association of these cell types at sites of inflammation and the high 11β-HSD1 activity that each cell type expresses. A possible paracrine interaction between these cells was thus explored in \textit{in vitro} co-culture experiments with FLS and macrophages isolated from either WT or 11β-HSD1 knockout mice. It was shown that 11β-HSD1 knockout macrophages had similar induction

![Figure 3](https://joe.bioscientifica.com)

**Figure 3**

Importance of 11β-HSD1 enzyme activity in bone and joint disease. Findings in mouse models of 11β-HSD1 deletion. Phenotypic effects are described in non-inflammatory and inflammatory states relating to bone and joint health. KO, knockout mice; WT, wildtype mice.
of glucocorticoid target genes to WT macrophages in response to incubation with conditioned media from WT FLS cells treated with DHC. However, conditioned media from 11β-HSD1 knockout FLS cells treated with DHC failed to induce target genes in either WT or 11β-HSD1 knockout macrophages. Similar results were seen when conditioned media from macrophages treated with DHC was incubated with FLS cells with glucocorticoid responsive genes only being induced with conditioned media from WT and not 11β-HSD1 knockout macrophages. These results indicate that 11β-HSD1 can mediate paracrine GC-signalling interactions between these cell populations which are present at sites of inflammation. Importantly from a clinical perspective, these results suggest that expression of 11β-HSD1 in either mesenchymal or myeloid cells is sufficient to permit the anti-inflammatory effects of glucocorticoids, and that any attempt to block these actions would require enzyme inhibition in both these tissue types.

Subsequent studies have examined some of the cellular specificity of 11β-HSD1 action in mediating the beneficial and adverse impacts of therapeutic glucocorticoids on bone and muscle. Therapeutic glucocorticoids have been widely used in a clinical setting to reduce the development of bone erosions and joint destruction in rheumatoid arthritis. This bone loss is due to excessive activity of osteoclasts, the bone-resorbing cells. These cells belong to the myeloid lineage but require signals from mesenchymal cells (osteoblasts or FLS cells) to differentiate and function. It is unclear whether therapeutic glucocorticoids inhibit osteoclastic activity in arthritis through direct actions on osteoclasts and their precursors or through effects on mesenchymal cells. As described above, mouse models of chronic polyarthritis develop bone erosions and joint destruction that is preventable by treatment with systemic corticosterone treatment. Mice with mesenchymal deletion of 11β-HSD1 had a similar protection against joint destruction and bone loss when treated with corticosterone compared to WT mice (Fenton et al. 2022). However, mice with myeloid (and thus osteoclast) deletion of 11β-HSD1 were resistant to the bone protective actions of corticosterone where increased osteoclastic bone resorption and joint destruction were seen. In in vitro studies, osteoclasts that were generated from peripheral blood mononuclear cells from healthy human donors expressed 11β-HSD1 and this activity was increased by treatment with inflammatory cytokines. Treatment with the inactive glucocorticoid cortisone was able to significantly inhibit the bone resorption capacity of human osteoclasts indicating a functional role for 11β-HSD1 activity in osteoclasts. These data suggest that 11β-HSD1 expression and activity within the osteoclast, rather than the mesenchymal population, is important for inflammation-induced bone loss and the suppression of inflammatory bone loss in response to therapeutic glucocorticoids.

Implications for use of glucocorticoids in inflammatory states

The studies presented above indicate that reactivation of glucocorticoids is an important, and perhaps critical, feature of the effectiveness of commonly used therapeutic glucocorticoids for bone and joint inflammatory conditions and likely many other conditions. During various types of inflammation, local expression of 11β-HSD1 has an important function to increase the action of glucocorticoids in specific target tissues and thus reduces the amount of glucocorticoid exposure needed to tissues that do not express 11β-HSD1. The advantage of these glucocorticoids is likely proportional to the degree of 11β-HSD1 expression and how selective at a cellular level the selection is. In effect, cells that can induce 11β-HSD1 expression in response to inflammation develop a degree of ‘inflammation selective activation’ of endogenous and therapeutic glucocorticoids. Some adverse effects in tissues are also likely to relate to prolonged very high exposure of cells and tissues to glucocorticoids through 11β-HSD1 activity and it is no surprise that many of the long-term adverse effects of glucocorticoids are most obvious in tissues known to express high levels of 11β-HSD1 such as skin, adipose tissue, bone and muscle.

A possible focus of drug design might be to try to enhance the degree to which glucocorticoids are maintained in their inactive form so as to allow only the effects due to local recycling by 11β-HSD1. However, in vivo, the liver is a major site of 11β-HSD1 expression and appears to have a major function of reactivating inactive glucocorticoids present in the circulation that have been generated by 11β-HSD2 predominantly in the kidney. This high activity also explains why prednisone and prednisolone have equivalent actions when given orally, with prednisone efficiently converted to prednisolone on the first pass through the liver (Uribe et al. 1982). Strategies that might be employed to keep glucocorticoids in an inactive form might include encapsulated/liposomal formulations (which might also have the additional
advantage of selective release at sites of inflammation) or the use of topical forms where practical, for example, in skin disorders. Neither of these approaches has yet been examined.

The importance of the 11β-position of the glucocorticoid structure in mediating the effects of glucocorticoids in vivo might also explain some of the problems encountered in the development of selective glucocorticoid receptor agonists (SEGRAs). Many non-steroidal molecules have been demonstrated to be effective GR agonists in vivo, but without the ability to be recycled selectively in tissues, these agents are likely to struggle to have a similar ‘therapeutic index’ to current oral glucocorticoids. This is even if they have potentially superior features relating to how these interact with various post-receptor responses which might reduce adverse actions. Most studies examining systemically administered SEGRAs have had disappointing clinical results, although the notable exception is fosdagrocorat which has shown promise in the context of treatment of patients with rheumatoid arthritis (Buttgereit et al. 2019). Given its non-steroidal structure, fosdagrocorat, or its active metabolite, are unlikely to be substrates for 11β-HSD enzymes, but this has not yet been examined experimentally.

Insights into the importance of the 11beta-position are likely to come from studies of a novel glucocorticoid vamorolone (Heier et al. 2019, Liu et al. 2020). This glucocorticoid has the unusual property of not having a hydroxy-carbonyl group at the 11 position, and thus it is not a substrate for either 11β-HSD1 or 11β-HSD2. The structural differences of vamorolone, cortisol, prednisone, prednisolone and the pure GR agonist dexamethasone are illustrated in Fig. 4. Many glucocorticoids that lack such an 11beta-group would have the problem that they would not be inactivated by 11β-HSD2 in the kidney and thus could potentially bind unopposed to the mineralocorticoid receptor leading to hypertension. However, vamorolone behaves as a mineralocorticoid receptor antagonist rather than an agonist (Heier et al. 2019) and so avoids the issue of hypertension. Vamorolone has shown promising results in the setting of Duchenne muscular dystrophy (DMD) where glucocorticoids such as prednisone have previously been shown to preserve muscle fibre health when given in high dosage (Mendell et al. 1989). Clinical studies suggest that vamorolone has similar muscle protective effects compared to prednisone/prednisolone but with less side effects on tissues such as fat and bone (Mah et al. 2022). Some of these differences could relate to some of the dissociate properties that vamorolone displays at a receptor level (Liu et al. 2020), but this could also suggest that in some conditions avoiding the 11β-HSD1-mediated reactivation of glucocorticoids in some tissues could give the same anti-inflammatory effect without the adverse effects. Along similar lines, the systemic use of 11β-HSD1 inhibitors has been proposed in patients with endogenous Cushing’s disease, for example, due to pituitary or adrenal tumours (Morgan et al. 2014), and this has been examined in one clinical trial published to date where an 11β-HSD1 inhibitor reduced body fat and increased muscle mass in patients with Cushing’s syndrome due to autonomous

![Image of molecular structures](https://joe.bioscientifica.com)

**Figure 4**

Molecular structures of cortisol (referred to as hydrocortisone when administered as a pharmaceutical) and the synthetic glucocorticoids prednisone, prednisolone, dexamethasone and vamorolone. Differences in the 11β-position of the steroid ring are noted between glucocorticoids.
cortisol production (Oda et al. 2021). Given that the adverse effects of glucocorticoids also depend on reactivation by 11β-HSD1, systemic inhibition of the enzyme should minimise the adverse effects due to reactivation. In the particular situation of DMD, the target of glucocorticoid treatment is not a typical inflammatory reaction but rather myocyte membrane fragility and necrosis due to a lack of the dystrophin protein. Interestingly, muscle tissue and cultured myocytes from mouse models of DMD demonstrated the presence of 11β-HSD2. Importantly, levels of 11β-HSD2 in myocytes derived from mouse models of DMD were significantly increased and the level of expression correlated with the degree of severity of the DMD mouse models. It is thus possible that the superiority of vamorolone over prednisone/prednisolone might be due to some local inactivation of prednisolone by 11β-HSD2 within dystrophic muscles, something that cannot happen with vamorolone due to its lack of the hydroxy-carbonyl group at the 11 position of the steroid ring. Studies with vamorolone and clinical experience with orally administered dexamethasone (which has powerful anti-inflammatory actions and adverse effects) thus illustrate that 11β-HSD1 activity is not essential for glucocorticoids to have anti-inflammatory activities. It appears that the ‘ideal’ glucocorticoid may differ greatly depending on the underlying condition being targeted. It should also be recognised that some of the assumptions regarding glucocorticoid physiology might change in particular disease states, for example, clearance of cortisol/hydrocortisone at a systemic level is dramatically reduced during severe critical illness (Boonen et al. 2013).

Conclusions

Tissue metabolism of glucocorticoids allowing for selective amplification of glucocorticoid at a tissue level introduces a level of complexity to glucocorticoid action that has not been fully appreciated until now. Much of the complexity and subtlety of action appears to occur at a level prior to the binding of glucocorticoids to the GRs. This knowledge can potentially explain some of the differences seen in glucocorticoid actions in a clinical setting and in particular the resilience of some of the earliest therapeutic glucocorticoids such as prednisone and prednisolone despite decades of attempts to improve on them. This information might also be used to better target glucocorticoids, for instance, using glucocorticoids capable of recycling in situations where the tissue being targeted is known to express 11β-HSD1 or, conversely, avoiding these glucocorticoids in situations where the target tissue has no 11β-HSD1 expression or expresses 11β-HSD2. Given that 11β-HSD1 expression in tissues can change in response to inflammation, this information might also be used to guide the duration or dose of glucocorticoids used in specific situations. The recognition that to a large extent the inactive counterpart of these glucocorticoids is more important to anti-inflammatory effects than the active glucocorticoid presents novel opportunities to more selectively target glucocorticoids to tissues or to reduce the likely side effects.

Declaration of interest

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References


Cobice DF, Livingstone DEW, McBride A, MacKay CI, Walker BR, Webster SP & Andrew R 2018 Quantification of 11beta-hydroxysteroid dehydrogenase 1 kinetics and pharmacodynamic effects of inhibitors in brain using mass spectrometry imaging and stable-isotope tracers in...


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nervous system? *Arthritis and Rheumatism* **52** 1711–1720. ([https://doi.org/10.1002/art.21091](https://doi.org/10.1002/art.21091))

Uribe M, Summerskill WH & Go VL 1982 Comparative serum prednisone and prednisolone concentrations following administration to patients with chronic active liver disease. *Clinical Pharmacokinetics* **7** 452–459. ([https://doi.org/10.2165/00003088-198207050-00005](https://doi.org/10.2165/00003088-198207050-00005))


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