The role of pre-receptor glucocorticoid metabolism in chronic inflammatory disease-associated muscle atrophy

Citation for published version (APA):

Document status and date:
Published: 01/01/2023

DOI:
10.26481/dis.20230329jw

Document Version:
Publisher's PDF, also known as Version of record

Please check the document version of this publication:

• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
• The final author version and the galley proof are versions of the publication after peer review.
• The final published version features the final layout of the paper including the volume, issue and page numbers.

Link to publication

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
  • You may not further distribute the material or use it for any profit-making activity or commercial gain
  • You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license above, please follow below link for the End User Agreement:
www.umlib.nl/taverne-license

Take down policy
If you believe that this document breaches copyright please contact us at:
repository@maastrichtuniversity.nl
providing details and we will investigate your claim.

Download date: 01 Oct. 2023
8.5 **Glucocorticoids continue to be an essential clinical tool in Chronic Inflammatory Diseases**

Glucocorticoids (GCs) are a family of steroid hormones and their synthetic therapeutic derivatives that possess potent anti-inflammatory and immunomodulatory properties. Endogenous GCs represents an essential component of the innate stress response, where they suppress inflammation and tissue damage in response to injury and infection, whilst therapeutic GCs play a major role in the management of a wide array of inflammatory diseases through their suppression of inflammation and disease activity. To date 7% of the population over 65 years old receives GCs in the UK, where they account for 1/30 of all prescriptions and represent a global market worth over £10 billion per year [1]. Unfortunately, their application is limited by severe off target side effects, including increased cardiovascular disease, insulin resistance, osteoporosis and muscle wasting that reduces quality of life [2, 3].

Glucocorticoids are frequently utilised in the management of chronic inflammatory diseases (CIDs) such as rheumatoid arthritis (RA) and chronic obstructive pulmonary disease (COPD). Rheumatoid arthritis is an autoimmune disorder characterised by progressive joint destruction and synovitis [4] affecting 1-2% of the global population, and is frequently accompanied with extra-articular metabolic complications such as muscle wasting, osteoporosis, and increased cardiovascular mortality [5, 6]. Similarly, COPD is a progressive lung disorder characterised by chronic lung inflammation and irreversible remodelling of the airways is also associated with extra-pulmonary comorbidities and represents the third leading cause of death worldwide by the WHO [7]. As with RA patients, these include increased risk of metabolic co-morbidities such as muscle wasting, which affect 20-40% of emphysematous COPD patients [8, 9]. Endogenous GCs have been proposed to be an important driver of metabolic musculoskeletal complications associated with CIDs. Both RA and COPD are associated with low grade inflammation and muscle wasting, in addition, disease flare ups are also associated with higher levels of myopathy [5, 10]. Endogenous glucocorticoid excess has been proposed to be an important driver of this comorbidity [11, 12]. In this context, clinical studies have identified that patients with severe disease activity have a dysregulated hypothalamic-pituitary-adrenal (HPA) axis, characterised by reduced overall cortisol levels [13] and dampened cortisol responses with Corticotropin-Releasing
In particular, several central studies have revealed that local and systemic activation of GCs, particularly in the joints and muscle of RA patients, via the 11 beta-hydroxysteroid dehydrogenase 1 (11β-HSD1) enzyme are potent drivers of localised tissue specific endogenous GC excess [15, 16]. Therapeutic GCs are also commonly used to treat exacerbations of both RA and COPD. In COPD, they coincide with reduced hospital stays and faster recovery of lung function [17], however even short-term therapy with GCs were shown to suppress HPA axis function in up to 63% of patients with exacerbations [18], which may contribute to muscle wasting in these patients [19].

Muscle wasting is an independent predictor of increased exacerbations in COPD, flare-ups in RA, and poorer prognostic outcomes and increased mortality [5, 20]. Therefore, the cycle of worsened disease activity leading to muscle wasting, which ultimately results in worsened disease activity, needs to be addressed in clinical settings when treating patients with COPD and RA. Despite the concerns that GCs may be a central component of metabolic features of chronic inflammatory disease, they continue to be widely utilised in their management due to their potent anti-inflammatory properties.

8.6 As a central gatekeeper of glucocorticoid action, 11β-HSD1 is a potential target for modulation of GC side effects.

Glucocorticoids actions on peripheral tissues are highly regulated by their metabolism via 11β-HSD1, which primarily catalyse the interconversion of inactive GCs to their active counterparts (cortisone to cortisol in humans; 11-dehydrocorticosterone to corticosterone in rodents). Expressed in abundance in the liver, bone, adipose tissue and skeletal muscle, 11β-HSD1 is a central intracellular gatekeeper of glucocorticoid amplification and action within tissues and is potently upregulated in response to elevated GCs and inflammation [21-23]. Indeed, multiple studies have identified that local activation of GCs by 11β-HSD enzymes can mediate a greater impact on disease activity and related comorbidities than elevated systemic levels of GCs alone [24]. Consequently, 11β-HSD1 has been a focal point as a potential therapeutic target for alleviating the deleterious manifestations and undesirable side effects of GCs in metabolic disorders such as hypertension, insulin resistance, dyslipidaemia and steatosis where GC excess is implicated as driver of disease [24-26]. Preclinical studies in mice models supported this concept, with
transgenic deletion of 11β-HSD1 in mice protecting from GC excess-induced hyperinosaemia, hepatic steatosis, adiposity, hypertension and myopathy [27]. Further encouraging evidence was provided from early clinical studies using the non-selective 11β-HSD1 inhibitor carbenoxolone (CBX) [28]. This inhibited GC-mediated lipolysis characterised by reduced prednisolone-induced glycerol release. CBX also showed promising reductions in glycolysis in patients with type 2 diabetes and reduced cholesterol levels in healthy patient cohorts [29]. These studies highlighted the importance of local activation of GCs by 11β-HSD1, whilst raising the possibility of 11β-HSD1 inhibitors to manage the features of metabolic disease. Unfortunately, the absence of enzyme specificity with drugs such as CBX resulted in off target side effects such as elevated blood pressure and electrolyte imbalance, as a result of off target renal 11β-HSD2 inhibition, which increased MR signalling [30].

However, these studies fuelled academic and industry interest in therapeutic 11BHSD1 inhibitors in the management of metabolic diseases, such as type 2 diabetes and polycystic ovary syndrome (PCOS) and resulted in a plethora of highly selective compounds. Selective inhibitors such as MK-0916, INCB13739 and AZD4017 have since been developed. Patients with type 2 diabetes treated with MK-0916 and INCB13739 have significant reductions in blood pressure, average blood glucose and triglyceride levels [31, 32]. Despite their improved specificity, efficacy and tolerance, their inability to exceed or outperform standard clinical treatments of these disorders, has stagnated their progression beyond phase II clinical trials, and subsequent application in metabolic diseases. Exploring alternative disease conditions where 11β-HSD1 inhibitors may be beneficial beyond obesity and type-II diabetes, one study showed 11β-HSD1 inhibition by AZD4017 in patients with Idiopathic Intracranial Hypertension improved lipid profiles, markers of hepatic function. Interestingly, an increase in lean muscle mass was also documented in this study, correlating with elevated levels of circulating androgens [33]. This positive effect of 11β-HSD1 inhibition on muscle mass was further confirmed in a preclinical model in which mice null for the enzyme were protected against the GC excess-induced muscle loss [27]. These data identify 11β-HSD1 as a potential therapeutic target in mediating muscle wasting.
8.7 **11β-HSD1 as a driver of muscle wasting in CID and therapeutic corticosteroid excess**

As discussed, previous research has shown 11β-HSD1 is also up-regulated in response to inflammatory cytokines [21-23], including in skeletal muscle, and systemic inhibition of 11β-HSD1 may therefore alleviate GC-driven muscle wasting in CIDs. Moreover, such approach would mostly reduce local GC increases in tissues with otherwise characterized by higher levels of 11β-HSD1 such as skeletal muscle [34]. However, in our AE-COPD model we found deletion of 11β-HSD1 combined with pulmonary inflammation significantly further increased circulating levels of corticosterone (chapter xxx), indicative of a lack of HPA axis regulation. The selective 11β-HSD1 inhibitor BI 187004 showed an increase of adrenocorticotropic hormone (ACTH) and ultimate increase in HPA axis activity in overweight or obese, healthy males [35]. These findings are in line with the lack of HPA axis regulation seen in our model with elevated corticosterone levels in LPS treated 11β-HSD1/KO mice. Therefore investigation into the long-term side effects of the use of 11β-HSD1 inhibitors would be required, as consequences for HPA axis regulation must first be evaluated [36]. Despite these findings, many of the studies investigating HPA dysregulation and 11β-HSD1 inhibition focus on metabolic diseases, as such, there are few studies that explore 11β-HSD1 inhibition in inflammatory diseases where inflammatory cytokines greatly impact HPA axis homeostasis. In contrast, in our model of RA, utilising the TNF-tg mouse model of polyarthritis, therapeutic GC excess combined with genetic 11β-HSD1 deletion showed partial protection against GC-induced muscle wasting (Chapter 6), highlighting adjunct therapies in this setting may be beneficial.

8.8 **Future directions and how 11β-HSD1 inhibitors can be used in CID**

Inhibitors of 11β-HSD1 have shown great potential in treatment of metabolic disorders, however many of these studies fail to address their possible impact in CIDs. Our data show inhibition of 11β-HSD1 during AE-COPD (Chapter 3) had detrimental effects on skeletal muscle in this setting, however, deletion of 11β-HSD1 in combination with GC therapy in a model of RA (Chapter 6) was beneficial to prevent GC-induced muscle wasting. In addition, resistance to the anti-inflammatory actions of GCs were shown with 11β-HSD1 inhibition in polyarthritic mice, highlighting possible detrimental effects of the use of 11β-
HSD1 inhibitors in this setting. Following up these findings in other stages of CIDs would be of important value in determining the efficacy of 11β-HSD1 inhibitors. Further research into combined 11β-HSD1 deletion with GC treatment in a model of AE-COPD may highlight their potential as an adjunct therapeutic strategy, which is highly relevant to address, as glucocorticoids are currently still standard treatment for moderate to severe AE-COPD. Additionally, repeat exacerbations of disease are associated with increased muscle wasting and therefore should be incorporated into study designs. Glucocorticoid metabolism-modulating agents with tissue specific actions have the potential to be exploited as adjunct therapy to increase the therapeutic index of GC administration, which is the current standard of care in the treatment of CIDs like AE-COPD and RA. Data shown in Chapter 3 suggest 11β-HSD1 inhibition may not be a suitable therapeutic intervention alone to modulate endogenous GC-driven muscle wasting in AE-COPD, however in settings where GCs are applied therapeutically, 11β-HSD1 inhibitors may alleviate the undesirable side effects caused by GCs, such as muscle wasting. Alternatively, applying 11β-HSD1 inhibitors, rather than genetic deletion, across CID settings such as RA, COPD and chronic kidney disease (CKD) will improve the understanding of the mechanisms underpinning muscle wasting in these settings with increased clinical translatability, as it will allow timing and dosing of 11β-HSD1 inhibitors. Whilst GCs are commonly used in treatment of CIDs, high-dose GCs are often given during exacerbations of disease, therefore focus on duration of and dose of GCs in these settings should be considered. For instance, in our RA model of 11β-HSD1 deletion combined with GC excess, a partial protection of muscle wasting was observed, however, an important factor to determine would be if 11β-HSD1 inhibitors and combined GC therapy in RA patients, administered at the time of flare up, result in similar protection of muscle loss. Utilising global 11β-HSD1/KO animals in these studies provides translatability of 11β-HSD1 inhibitors as therapeutics, however, using inhibitors would also allow for selective inhibition periods. For example, combined GC therapy with 11β-HSD1 inhibition specifically during flare ups or exacerbations, which may circumvent HPA dysregulation or deleterious side effects of continuous 11β-HSD1 inhibition, which ultimately may contribute to skeletal muscle wasting.

11β-HSD1 inhibitors could be considered for clinical application of CIDs when combined with GC treatment, as demonstrated in Chapter 6. However, as endogenous GC
levels may be risen as well, the findings of Chapter 3 suggest that 11β-HSD1 inhibitors could exacerbate muscle wasting in CIDs, making their application in this setting is less clear. This could be investigated with further studies into the phases of disease such as early onset vs established disease, timing of inhibitors, in addition to timing and dose of GCs. These data could provide opportunity for expanded treatment options for the 1-3% of the population who are solely looking at therapeutic GCs as treatment options globally [37]. While effective treatment to reduce skeletal muscle wasting in these patients currently remains an unmet medical need, the novel insights provided by the work in this thesis contribute to the fundamental understanding of GC-driven muscle wasting and identified further leads for investigating 11β-HSD1 inhibitors in this context.
References


