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

Abstract

Chronic inflammatory diseases (CIDs) such as rheumatoid arthritis (RA) and chronic obstructive pulmonary disease (COPD) are associated with prolonged periods of local and systemic inflammation. As a result, patients with CIDs often encounter co-morbidities such as osteoporosis and skeletal muscle wasting. Glucocorticoids (GCs) are steroid hormones widely used in the treatment of CIDs due to their potent anti-inflammatory effects. Despite their efficacy, their clinical application is limited due to undesirable side effects including osteoporosis and muscle wasting. The enzyme 11 beta-hydroxysteroid dehydrogenase 1 (11β-HSD1) is found in abundance in tissues such as skeletal muscle and bone and converts inactive GCs to their active counterparts, increasing local GC activity. In this thesis we look at the contribution of 11β-HSD1 in mediating GC-induced muscle wasting in RA and acute exacerbations of COPD (AE-COPD). Using mouse models of RA and AE-COPD, we look at the impact global genetic deletion of 11β-HSD1 has in muscle and bone loss with inflammation or GC-excess. In emphysematous animals with pulmonary inflammation, genetic deletion of 11β-HSD1 resulted in exacerbated muscle atrophy in addition to increased corticosterone levels compared to wild-type (WT) controls. Mice with genetic overexpression of human TNF-α (TNF-tg) receiving corticosterone demonstrated a marked increase in muscle wasting compared to untreated mice. In contrast, a partial protection against muscle wasting was observed in 11β-HSD1 null mice with GC-treated polyarthritis. Taken together, our data suggest 11β-HSD1 inhibition in AE-COPD and RA may not protect against endogenous GC-driven muscle wasting, however when combined with therapeutic GCs, 11β-HSD1 inhibition may offer protection against muscle wasting in such disease settings.