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Review

Glucocorticoids, bone and energy metabolism

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ABSTRACT

Prolonged exposure to excessive levels of endogenous or exogenous glucocorticoids is associated with serious clinical features including altered body composition and the development of insulin resistance, impaired glucose tolerance and diabetes. It had been assumed that these adverse effects were mediated by direct effects of glucocorticoids on tissues such as adipose or liver. Recent studies have however indicated that these effects are, at least in part, mediated through the actions of glucocorticoids on bone and specifically the osteoblast. In mice, targeted abrogation of glucocorticoid signalling in osteoblasts significantly attenuated the changes in body composition and systemic fuel metabolism seen during glucocorticoid treatment. Heterotopic expression of osteocalcin in the liver of normal mice was also able to protect against the metabolic changes induced by glucocorticoids indicating that osteocalcin was the likely factor connecting bone osteoblasts to systemic fuel metabolism. Studies are now needed in humans to determine the extent to which glucocorticoid induced changes in body composition and systemic fuel metabolism are mediated through bone.

This article is part of a Special Issue entitled Bone and diabetes.

Contents

1. Introduction

The prolonged use of therapeutic glucocorticoids is associated with a range of adverse effects (Fig. 1). The detrimental effects on bone have received the greatest focus and there are now a range of therapeutic strategies available to reduce the negative effects of glucocorticoids on bone [1]. Endogenous or exogenous glucocorticoid excess is also associated with other serious clinical features such as the development of insulin resistance, impaired glucose tolerance and frank diabetes [2]. Glucocorticoids also cause changes in fat distribution favouring accumulation of central (visceral) fat at the expense of subcutaneous adipose tissue. Traditionally it has been thought that these adverse effects were mediated by direct effects of glucocorticoids on adipose tissue or the liver. Recent studies have questioned the role of these tissues in the abnormal energy metabolism associated with glucocorticoid excess [3–5]. At the same time other studies have indicated that these effects are, at least in part, mediated through the actions of glucocorticoids on bone [6].

1.1. Actions of glucocorticoids on energy metabolism

Long term glucocorticoid treatment of humans or experimental animals leads to an increase in insulin resistance manifested as a reduced

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Glucocorticoids: Therapeutic and adverse effects

Therapeutic actions	Adverse effects
Anti-inflammatory	Osteoporosis/osteonecrosis
Immunosuppression	Infections
Anti-allergic	Insulin resistance/Diabetes
Disease modification	Abnormal fat distribution
Increased vascular tone	Myopathy
Reduced oedema (cancer)	HPA axis suppression
Anti-proliferative (cancer)	Skin thinning
	Hypertension

Fig. 1. Illustration of the main therapeutic benefits and adverse effects of systemic glucocorticoid therapy.

ability of insulin to suppress endogenous glucose production (reviewed in [7]). Short term treatment with glucocorticoids is associated with impaired release of insulin from the pancreas but this action is not prominent during long term glucocorticoid use [3,8–10]. In clinical studies, patients with rheumatoid arthritis chronically treated with prednisolone tend to develop insulin resistance [8]. For most individuals blood glucose levels remain in the non-diabetic range but this is only achieved through a rise in plasma insulin levels. However, a significant proportion of glucocorticoid-treated individuals will develop glucose intolerance or diabetes mellitus. These patients tend to be those that already have a degree of insulin resistance due to their age, genetic or ethnic background, or other co-morbidities [11]. Many patients exposed to high doses of therapeutic glucocorticoids for prolonged periods develop also changes in the distribution of fat but there is a great variation in the degree to which this occurs between individuals. The basis for the changes in fat redistribution is unclear but differences in the response to glucocorticoids of subcutaneous and visceral adipose tissue have been proposed [2].

1.2. Molecular actions of glucocorticoids

The action of glucocorticoids in a particular tissue is regulated by both receptor and 'pre-receptor' mechanisms. As steroid hormones, glucocorticoids are able to pass across cell membranes. They are thought to primarily exert their effects by binding to specific intracellular receptors (glucocorticoid receptors). The ability of glucocorticoids to bind to their receptors is regulated by intracellular enzymes that can convert glucocorticoids between active and inactive forms. The best characterised of

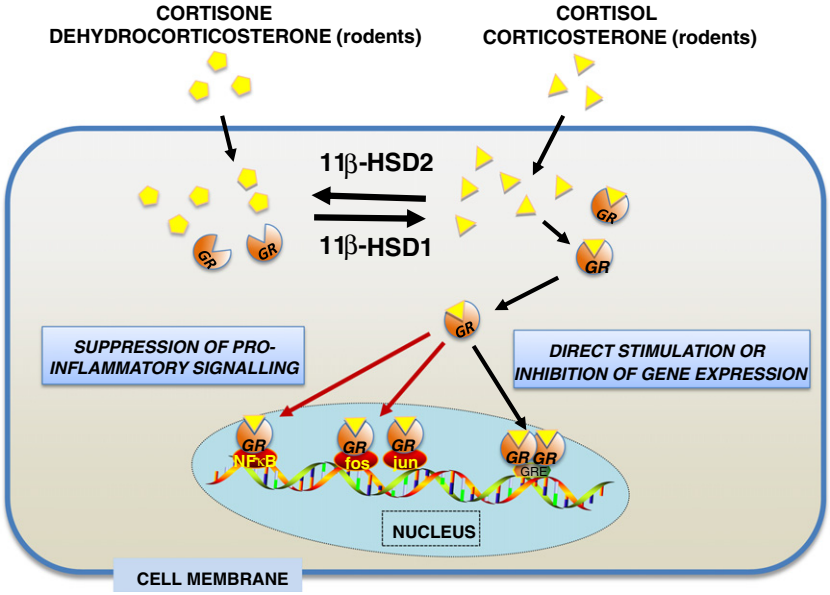

Fig. 2. Schematic overview of the action of glucocorticoids. Glucocorticoids are interconverted between inactive and active forms in the cytoplasm of target cells by the 11β-hydroxysteroid dehydrogenase (11β-HSD) enzymes. Active glucocorticoids when bound to glucocorticoid receptors (GR) can bind directly to glucocorticoid responsive elements to alter gene expression. Alternatively, glucocorticoid bound GR can interfere with the signalling of pro-inflammatory pathways such as nuclear factor kappa-B (NF-κB) or activator protein 1 (AP-1 — formed from fos and jun factors).