# Corticosteroids

## Mechanisms of Action in Health and Disease

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**KEYWORDS**

• Glucocorticoid • Glucocorticoid receptor • Glucocorticoid signaling
• Hypothalamic-pituitary-adrenal axis • Isoforms • Phosphorylation • Polymorphism

**KEY POINTS**

- An important challenge in the clinical application of glucocorticoids is the heterogeneity in glucocorticoid responsiveness among individuals with a significant portion of the population exhibiting some degree of glucocorticoid resistance.
- Glucocorticoid sensitivity and specificity is influenced by GR isoform expression profile. Inflammatory and pathologic processes modulate cellular GR isoform profiles.
- Assessing glucocorticoid sensitivity in individual patients is important for an optimal glucocorticoid treatment plan in the clinic.
- Understanding the heterogeneity of GR signaling in health and disease aids in the development of safer and more effective glucocorticoid therapies with improved benefit/risk ratios for patients.

### INTRODUCTION

Corticosteroids are a class of steroid hormones released by the adrenal cortex, which includes glucocorticoids and mineralocorticoids.[1] However, the term "corticosteroids" is generally used to refer to glucocorticoids. Named for their effect in carbohydrate metabolism, glucocorticoids regulate diverse cellular functions including development, homeostasis, metabolism, cognition, and inflammation.[2] Because of

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their profound immunomodulatory actions, glucocorticoids are one of the most widely prescribed drugs in the world and the worldwide market for glucocorticoids is estimated to be worth more than $10 billion per year.[3] Glucocorticoids have become a clinical mainstay for the treatment of numerous inflammatory and autoimmune diseases, such as asthma, allergy, septic shock rheumatoid arthritis, inflammatory bowel disease, and multiple sclerosis. Unfortunately, the therapeutic benefits of glucocorticoids are limited by the adverse side effects that are associated with high dose (used in the treatment of systemic vasculitis and systemic lupus erythematosus) and long-term use. These side effects include osteoporosis, skin atrophy, diabetes, abdominal obesity, glaucoma, cataracts, avascular necrosis and infection, growth retardation, and hypertension.[3]

Furthermore, patients on long-term glucocorticoid therapy also develop tissue-specific glucocorticoid resistance.[4] Understanding the molecular mechanisms underlying the physiologic and pharmacologic actions of glucocorticoids is of great importance because it may aid in developing synthetic glucocorticoids with increased tissue selectivity, which can thereby minimize the side effects by dissociating the desired anti-inflammatory functions from undesirable adverse outcomes. This article summarizes the recent advances and molecular processes involved in glucocorticoid action and function and discusses in detail the potential role of the glucocorticoid receptor (GR) in determining cellular responsiveness to glucocorticoids.

## GLUCOCORTICOID SYNTHESIS, SECRETION, AND BIOAVAILABILITY

Glucocorticoids (cortisol in humans and corticosterone in rodents) are steroid hormones synthesized and released by the adrenal glands in a circadian manner, in response to physiologic cues and stress.[5] The circadian profile of glucocorticoid release from the adrenal glands is regulated by the hypothalamic-pituitary-adrenal (HPA) axis. Inputs from the suprachiasmatic nucleus stimulate the paraventricular nucleus of the hypothalamus to release corticotrophin-releasing hormone and arginine vasopressin. These hormones act on the anterior pituitary where they activate corticotroph cells to secrete adrenocorticotrophin hormone (ACTH) into the general circulation. Subsequently, ACTH acts on the adrenal cortex to stimulate the synthesis and release of glucocorticoids (**Fig. 1**A).[6] Once released from the adrenal glands into the blood circulation, glucocorticoids access target tissues to regulate a myriad of physiologic processes, including metabolism, immune function, skeletal growth, cardiovascular function, reproduction, and cognition. Because of its lipophilic nature, glucocorticoids cannot be presynthesized and stored in adrenal glands, but have to be rapidly synthesized (using several enzymatic reactions) on ACTH stimulation. This feed-forward mechanism within the HPA system is balanced by negative feedback of glucocorticoids acting at the anterior pituitary and within the hypothalamus to inhibit further release of ACTH and corticotrophin-releasing hormone, respectively (see **Fig. 1**A).[7]

Biologically active glucocorticoids are synthesized from cholesterol through a multienzyme process termed steroidogenesis.[5,7] ACTH increases adrenal gland activity via protein kinase A activation leading to nongenomic regulation of steroidogenic proteins. This includes phosphorylation of hormone-sensitive lipase, a protein that increases the levels of intracellular cholesterol, and phosphorylation of steroidogenic acute regulatory protein, which promotes the transport of cholesterol into the mitochondria, where cholesterol is converted into pregnenolone by the enzyme side-chain cleavage cytochrome P-450. This process is followed by several enzymatic reactions within the mitochondria and the endoplasmic reticulum that ultimately leads