Review

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Feature Review

Glucocorticoid receptor signaling in health and disease

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Glucocorticoids are steroid hormones regulated in a circadian and stress-associated manner to maintain various metabolic and homeostatic functions that are necessary for life. Synthetic glucocorticoids are widely prescribed drugs for many conditions including asthma, chronic obstructive pulmonary disease (COPD), and inflammatory disorders of the eye. Research in the past few years has begun to unravel the profound complexity of glucocorticoid signaling and has contributed remarkably to improved therapeutic strategies. Glucocorticoids signal through the glucocorticoid receptor (GR), a member of the superfamily of nuclear receptors, in both genomic and non-genomic ways in almost every tissue in the human body. In this review, we provide an update on glucocorticoid receptor signaling and highlight the role of GR signaling in physiological and pathophysiological conditions in the major organ systems in the human body.

Glucocorticoids

Natural glucocorticoids (cortisol in humans and corticosterone in rodents) are cholesterol-derived hormones secreted by the zona fasciculata of the adrenal glands. The synthesis and release of glucocorticoids is under dynamic circadian and ultradian regulation by the hypothalamic–pituitary–adrenal (HPA) axis (Figure 1) [1]. Furthermore, the availability of natural glucocorticoids in tissues is regulated by corticosteroid-binding globulin in serum and by locally expressed 11β-hydroxysteroid dehydrogenase (11β-HSD) [2] enzymes (Figure 1). Imbalance in glucocorticoid levels such as chronic elevation or deficiency can result in pathological conditions known as Cushing's disease and Addison's disease, respectively.

Synthetic glucocorticoids are drugs that resemble natural glucocorticoids. Prednisone/prednisolone, dexamethasone, and budesonide are among the commonly prescribed glucocorticoids. Synthetic glucocorticoids differ from natural glucocorticoids by their potency and metabolic clearance. Unlike natural glucocorticoids, dexamethasone is not susceptible to inactivation by 11β-HSD2, thereby increasing its local availability [3]. Furthermore, unlike natural glucocorticoids, synthetic glucocorticoids do not bind corticosteroid-binding globulin and are thereby not susceptible to their regulation of available levels.

The clinical use of glucocorticoids dates back to the late 1940s, when Philip Hench successfully treated the symptoms of rheumatoid arthritis [4] with cortisone, for which he later received a Nobel Prize [5]. Since then, glucocorticoids have revolutionized the field of medicine; synthetic glucocorticoids are being prescribed for chronic inflammatory conditions including asthma, skin infections, and ocular infections as well as for immunosuppression in patients undergoing organ transplantation. In addition to their anti-inflammatory properties, corticosteroids have been exploited for their antiproliferative and antiangiogenic actions for the treatment of cancers [6].

Both natural and synthetic glucocorticoids transduce their actions by binding to the GR. In the absence of glucocorticoids, the GR resides in the cytoplasm bound to chaperone proteins such as heat shock protein 90 (hsp90). On ligand binding, the GR undergoes a conformational change that triggers its translocation to the nucleus, where it can exert its actions mainly through genomic (transactivation and transrepression) mechanisms. GR is the product of a single gene, *NR3C1*, located on chromosome 5q31–32 in humans, that undergoes alternative processing to yield multiple, functionally distinct subtypes of GR (Figure 2). Diversity in GR signaling comes from the actions of different glucocorticoid-response elements (GREs) and multiple receptor isoforms generated by alternative splicing and alternative translation initiation [7]. Additionally, multiple post-translational modifications (PTMs) including phosphorylation, acetylation, ubiquitination, and SUMOylation with small ubiquitin-related modifier proteins can alter the function of this transcription factor [8]. These mechanisms are summarized in Table 1.

Mechanism of GR signaling

The GR

The GR is a modular protein containing an N-terminal transactivation domain (NTD), a central DNA-binding domain (DBD), a C-terminal ligand-binding domain (LBD), and a flexible 'hinge region' separating the DBD and the LBD. The NTD has a strong transcriptional activation function (AF1), which allows for the recruitment of coregulators and transcription machinery. Among the 48

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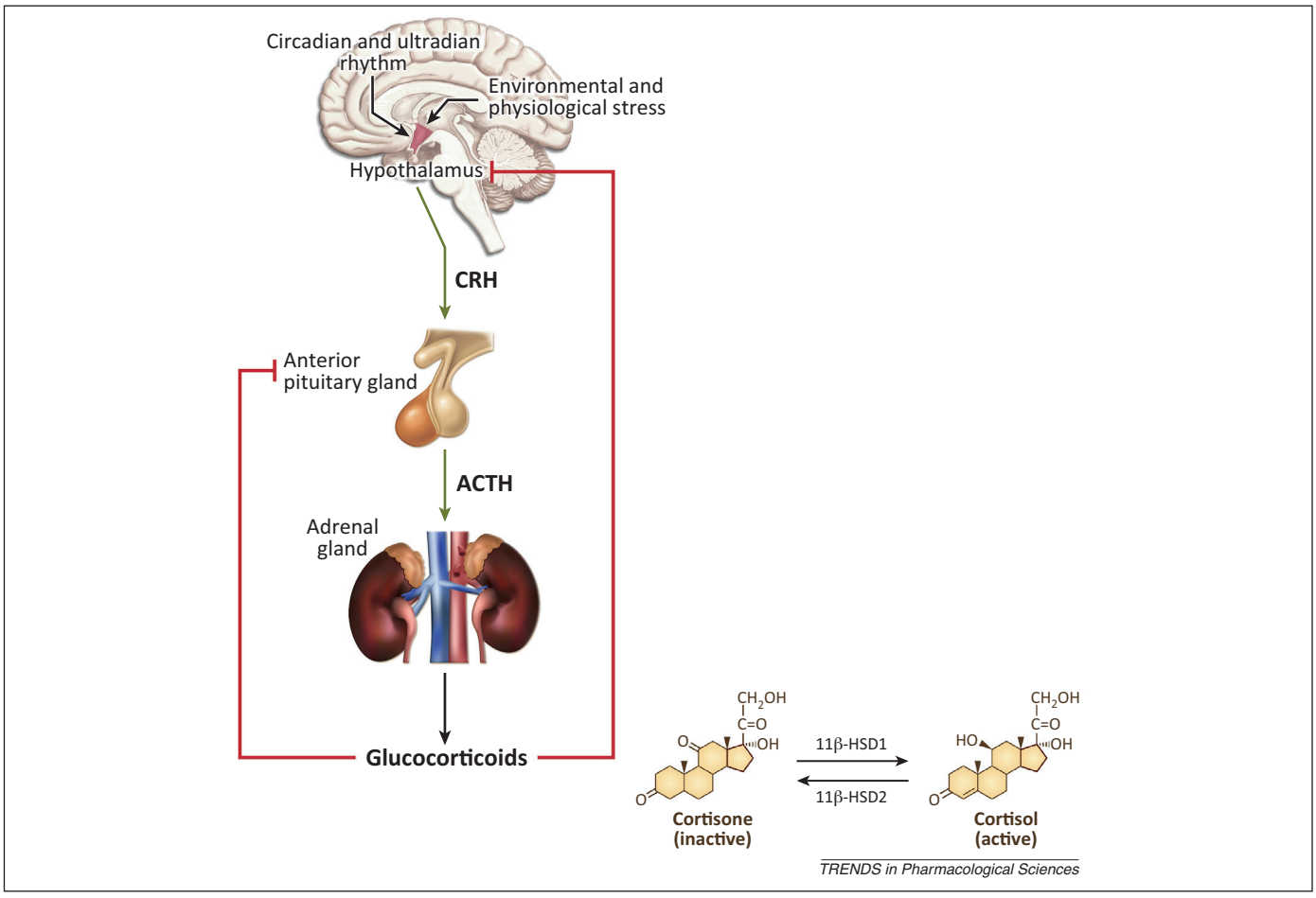

Figure 1. Schematic representation of the regulation of glucocorticoid levels by the hypothalamic–pituitary–adrenal (HPA) axis. Synthesis and release of glucocorticoids is under dynamic circadian and ultradian regulation by the periventricular nucleus of the hypothalamus. Corticotropin-releasing hormone (CRH) secreted by the hypothalamus stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. In turn, ACTH induces the synthesis and secretion of cortisol from the cortex of the adrenal glands into the bloodstream. In the blood, most of the cortisol remains bound to corticosteroid-binding globulins. The biologically active form of glucocorticoid is the unbound cortisol that can be converted to the inactive form, cortisone, by type 2 11β-hydroxysteroid dehydrogenase. Type 1 11β-hydroxysteroid dehydrogenase converts the cortisone to cortisol. Homeostasis in glucocorticoid levels is maintained by the negative-feedback loop suppressing ACTH levels in the anterior pituitary and CRH levels in the hypothalamus.

members of the nuclear receptor superfamily, the DBD is the most conserved region. The two zinc-finger motifs present in the DBD recognize and bind specific DNA sequences on target genes (GREs). On ligand binding, the second activation function (AF2), located in the LBD interacts with coregulators. The DBD/hinge region and the LBD each contain a nuclear localization signal that allows translocation to the nucleus via an importin-dependent mechanism [7].

GR isoforms

The human *NR3C1* gene contains nine exons with the protein-coding region formed by exons 2–9. Exon 1 forms the 5′-untranslated region. Alternative splicing of GR generates hGRα and hGRβ isoforms, which are identical through amino acid 727 but differ in their C termini [7]. The hGRα isoform binds to glucocorticoids, translocates to the nucleus, and recruits coregulators to exert transcriptional effects. However, the hGRβ isoform resides constitutively in the nucleus and acts as a natural dominant-negative inhibitor of the hGRα isoform. The hGRβ isoform can directly regulate genes that are not regulated by the hGRα isoform. Although hGRβ has not been reported to bind glucocorticoid agonists, one antagonist, RU486 (mifepristone), has been shown to bind to hGRβ and regulate its transcriptional activity [9]. These data show that hGRβ functions to negatively regulate the actions of the hGRα isoform as well as exert its own, independent functions. GRβ isoforms also exist in mice and zebrafish, but are generated by an alternative splicing mechanism that is distinct from the GRβ in humans [10,11]. GRγ, GR-A, and GR-P are other, less well-characterized GR isoforms that have been associated with glucocorticoid insensitivity [7]. For example, GRγ expression was found to be lower in patients with acute lymphoblastic leukemia who responded well to glucocorticoid treatment than in patients who responded poorly to the treatment [12].

The GRα isoform also undergoes alternative translation initiation in exon 2, generating eight additional isoforms of GR with truncated N termini (GRα-A, GRα-B, GRα-C1, GRα-C2, GRα-C3, GRα-D1, GRα-D2, and GRα-D3). GRβ may also generate eight β isoforms similar to hGRα [13]. All of the GRα isoforms have similar glucocorticoid-binding affinities and interactions with GREs. Interestingly, the GRα-C isoforms are the most biologically active and the GRα-D isoforms are the most deficient in glucocorticoid-mediated functions [14]. Intriguingly, the GRα-D isoform is constitutively present in the nucleus and

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