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Pathophysiology of Glucocorticoid Signaling

Physiopathologie de la signalisation glucocorticoïde

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Abstract

Glucocorticoids (GC), such as cortisol or dexamethasone, control various physiological functions, notably those involved in development, metabolism, inflammatory processes and stress, and exert most of their effects upon binding to the glucocorticoid receptor (GR, encoded by *NR3C1* gene). GC signaling follows several consecutive steps leading to target gene transactivation, including ligand binding, nuclear translocation of ligand-activated GR complexes, DNA binding, coactivator interaction and recruitment of functional transcriptional machinery. Any step may be impaired and may account for altered GC signaling. Partial or generalized glucocorticoid resistance syndrome may result in a reduced level of functional GR, a decreased hormone affinity and binding, a defect in nuclear GR translocation, a decrease or lack of DNA binding and/or post-transcriptional GR modifications. To date, 26 loss-of-function *NR3C1* mutations have been reported in the context of hypertension, hirsutism, adrenal hyperplasia or metabolic disorders. These clinical signs are generally associated with biological features including hypercortisolism without negative regulatory feedback loop on the hypothalamic-pituitary-adrenal axis. Patients had often low plasma aldosterone and renin levels despite hypertension. Only one GR gain-of-function mutation has been described associating Cushing's syndrome phenotype with normal urinary-free cortisol. Some GR polymorphisms (ER22/23EK, GR-9β) have been linked to glucocorticoid resistance and a healthier metabolic profile whereas some others seemed to be associated with GC hypersensitivity (N363S, *BclI*), increasing cardiovascular risk (diabetes type 2, visceral obesity). This review focuses on the earlier findings on the pathophysiology of GR signaling and presents criteria facilitating identification of novel *NR3C1* mutations in selected patients.

Keyword: *NR3C1*; Mutations; Glucocorticoid receptor; Glucocorticoid resistance; GR signaling

Résumé

Les glucocorticoïdes (GC) exercent de nombreux effets dans l'organisme, et sont impliqués dans le développement, le métabolisme, l'inflammation et le stress après liaison au récepteur des glucocorticoïdes (GR, codé par le gène *NR3C1*). Après activation par les GC, le complexe GC-GR est transféré dans le noyau où il s'homodimérise et se lie aux éléments de réponse sur l'ADN permettant la transcription de gènes cibles. La résistance aux GC peut être due à une altération de chacune des étapes de la signalisation du GR. À ce jour, 26 mutations perte de fonction du GR ont été rapportées devant des signes cliniques variés : hypertension artérielle, hirsutisme, hyperplasie surrénalienne ou troubles métaboliques. La plupart des patients ont un hypercortisolisme biologique sans rétrocontrôle négatif du cortisol sur l'axe hypothalamo-hypophyso-surrénalien. Les patients présentent également des concentrations plasmatiques d'aldostérone et de rénine normales ou basses, associées ou non à une hypertension artérielle. Chacune mutation altère la signalisation GC. Une seule mutation gain de fonction du GR a été décrite, conduisant à un profil métabolique défavorable (adiposité viscérale, diabète de type 2). Certains polymorphismes du GR (ER22/23EK, GR-9β) sont associés à une résistance partielle

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aux GC qui s'accompagne d'un meilleur profil métabolique. Enfin, d'autres polymorphismes (N363S, BclI) sont associés à une hypersensibilité GC et un profil métabolique plus défavorable. Cette revue résume les principales données récentes sur la physiopathologie du GR et présente les critères facilitant l'identification de nouvelles mutations du GR chez des patients sélectionnés.

Mots clés : NR3C1 ; Mutations ; Récepteur aux glucocorticoïdes ; Résistance aux glucocorticoïdes ; Signalisation glucocorticoïde

1. Introduction

Glucocorticoid hormones (GC) regulate many physiological functions such as stress responses, metabolism (lipid homeostasis), immunosuppressive effects (impacting dendritic cells and proinflammatory T lymphocytes, apoptosis) and hepatic functions by maintaining glucose homeostasis (gluconeogenesis and glycogenolysis), as well as growth, development and cell differentiation [1,2].

Owing to their impacts on immune system, synthetic GC are often used in auto-immune or inflammatory diseases. GC are steroid hormones, mostly synthesized by the adrenal gland cortex under the control of pituitary AdrenoCorticoTrophic Hormone (ACTH) and hypothalamic Corticotrophin Releasing Hormone (CRH). GC also exert a negative regulatory feedback loop on ACTH and CRH release [3].

Most of GC actions are mediated through binding to and activation of the nuclear glucocorticoid receptor (GR), even though some non-genomic actions have been reported to be mediated by a membrane-bound receptor event. This review will mostly focus on the mechanisms of GC action and their pathophysiologic disruption reported in humans, responsible for glucocorticoid resistance syndrome associated with the 26 GR loss-of-function mutations identified to date.

2. GR structure and function

The GR, encoded by the *NR3C1* gene, was cloned in 1985 [4]. GR is located on the chromosome 5 and belongs to the nuclear receptor superfamily, acting as a ligand-activated transcriptional factor [5]. *Human GR (hGR)* gene consists of ten exons from 1 to 9β. The first exon is an untranslated exon with seven alternative spliced untranslated first exons [6]. Exon 2 encoded for the entire N-Terminal Domain (Fig. 1) (395 aminoacids [aa]) and contained the coding sequence for the activating function 1 (AF-1) or tau 1 (τ1) domain (187–244 aa) that acts independently of ligand binding [7]. τ1 is a major transactivating domain, known to interact with coregulatory proteins or coregulators such as p160 family members, TIF2, DRIP/TRAP and SWI/SNF complex. Exons 3 and 4 encoded for the DNA Binding domain (DBD, ∼ 70 aa), which contains two zinc finger motifs. The first zinc finger harbors the proximal P-box, specified by 3 aa (Glycine^{439}, Serine^{440}, Valine^{443}), responsible for glucocorticoid responsive element (GRE) recognition [8] while the second zing finger harbors the D-box involved in homodimerization of receptor (5 aa: Aspartic acid^{458}, Glycine^{459}, Arginine^{460}, Asparagine^{461}, Alanine^{462}) localized at the N-terminus of the second zinc finger. Exons 5 to 9 encoded for the ligand binding domain (LBD), containing the tau 2 (τ2) domain, localized from 526 to 556 aa and an activating AF2 domain (753–768 aa), whose function is activated upon ligand binding [9]. The LBD interacts with an LXXLL motif also referred to as Nuclear Receptor (NR) box of coactivators. The LBD is a highly structured domain, composed of eleven alpha-helices (H1-H12, H2 is somehow absent) and 4 small beta strands. Helices H1 and H3 form one side of a helical sandwich pocket, while helices H7 to H10 compose the other side of this sandwich, helices H4, H5, H8 and H9 are present on the top of the ligand-binding pocket. A cavity in the bottom half, allows GC agonist molecule binding [10]. GR may exist in multiple isoforms generated by alternative splicing:

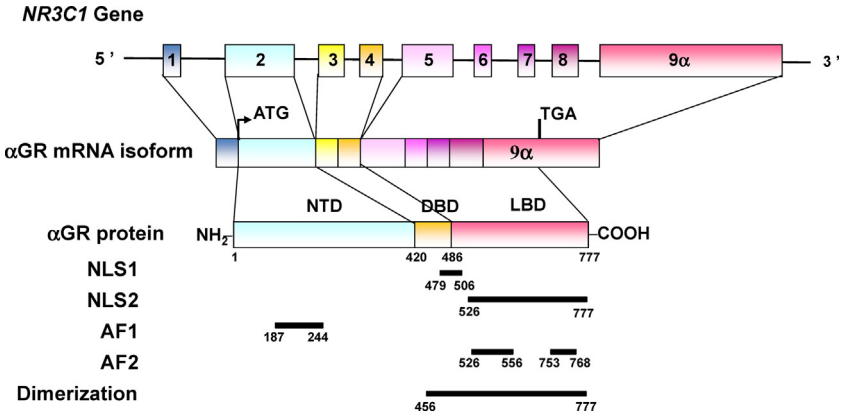

Fig. 1. Schematic representation of human *NR3C1* gene structure, mRNA and GR protein and its functional domains, adapted from Nicolaides et al., 2010 and Wallberg et al., 2000. AF: transactivation domain; DBD: DNA binding domain; LBD: ligand binding domain; NLS: nuclear localization signal; NTD: N-Terminal domain.

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