

Glucocorticoid Receptor β : View I

Alessandra Vottero and George P. Chrousos

Since the human glucocorticoid receptor (GR) cDNA and gene sequences were reported, the existence of two highly homologous GR isoforms was predicted. These were the classic human ligand-binding GR α , and a slightly smaller protein, termed GR β . Although the mechanism of action of GR α has been studied extensively, the role of GR β in the modulation of glucocorticoid actions remains uncertain.

Numerous biochemical events and cellular processes in virtually every tissue and organ of the body are influenced by glucocorticoids¹. These hormones are major effectors of basal and stress-related homeostasis; they regulate cardiovascular function and carbohydrate, protein and fat metabolism, suppress the immune/inflammatory response, and activate the central nervous system. In addition, glucocorticoids participate in the development and maturation of several organs and systems; for example, the adrenal medulla and the fetal lungs. These widespread and varying effects are mediated by specific intracellular receptor proteins of the steroid receptor family/nuclear receptor superfamily², the glucocorticoid receptors (GRs). Most of the metabolic effects of glucocorticoids are mediated primarily by interaction of the GR with glucocorticoid-response element (GREs) in the promoters of glucocorticoid-responsive genes. Their anti-growth and anti-inflammatory/immunosuppressive actions are mostly exerted via protein-protein interactions with positive regulators of growth and inflammation, such as the transcription factors activating protein 1 (AP-1) and nuclear factor κ B (NF- κ B), respectively.

A. Vottero and G.P. Chrousos are at the Section on Pediatric Endocrinology, DEB, NICHD, NIH, Bethesda, MD 20892, USA.

The existence of two highly homologous glucocorticoid receptor isoforms, which differ only at their C-termini, was predicted by the sequences of the human (h) GR cDNA and gene^{3,4}. These were the classic ligand-binding hGR α , and a slightly smaller protein, termed hGR β . Although the mechanism of action of hGR α has been studied extensively, the role of hGR β in the modulation of glucocorticoid receptor actions remains uncertain.

• Structure

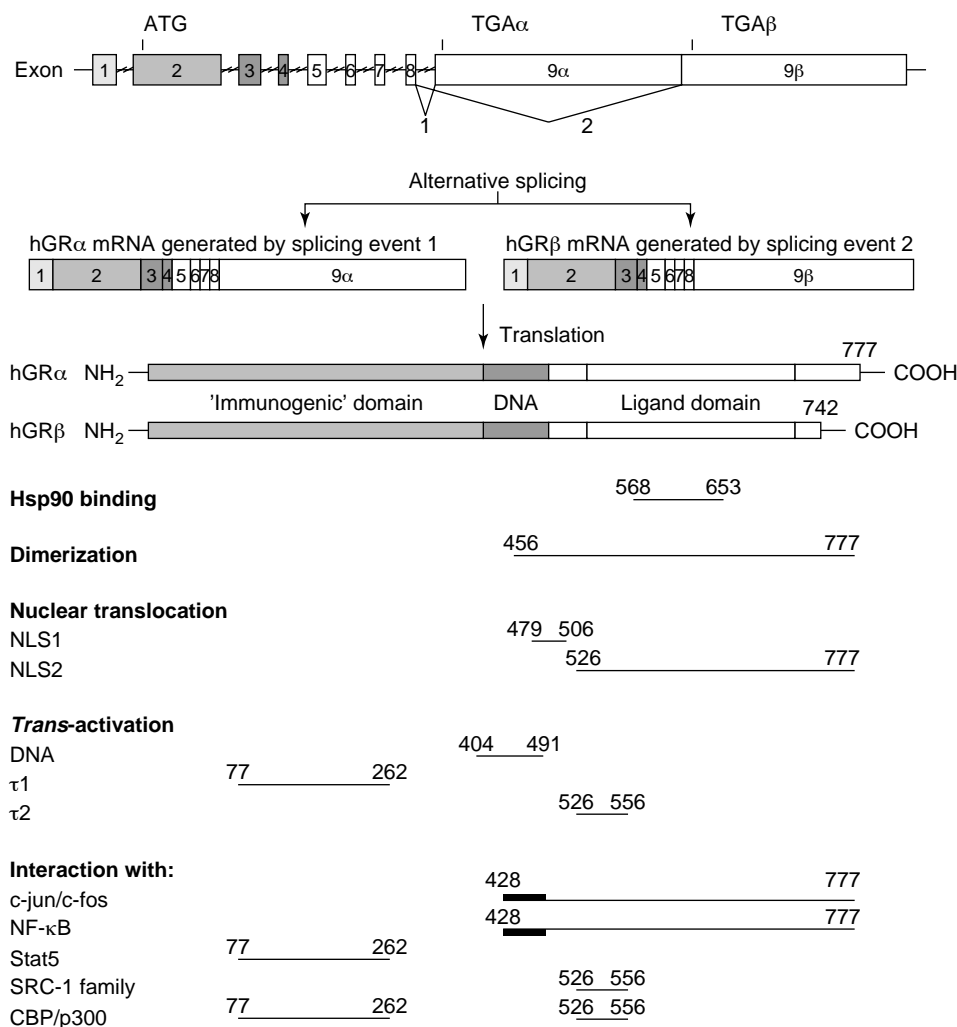
hGR α and hGR β are members of the nuclear receptor superfamily, which includes receptors for mineralocorticoids, androgens, progestins, estrogens, vitamin D, thyroid hormone, retinoic acids and other ligands, and a growing number of 'orphan' receptors, for most of which specific ligands have not been identified as yet^{5,6}. hGR α and hGR β are products of alternative splicing in exon 9 of the gene encoding hGR, which is located on chromosome 5 (Ref. 4). The first eight exons of the this gene contain the 5' non-coding and coding sequences common to both receptor isoform mRNAs, and exon 9 α and 9 β contain the coding and 3' non-coding sequences specific to hGR α and hGR β mRNAs, respectively (Fig. 1). Thus, these receptor isoforms are identical up to amino acid 727, but diverge

beyond this position, with hGR α having an additional 50 amino acids and hGR β an additional 15 non-homologous amino acids. The small difference in size is reflected in different molecular masses (~98 kDa for hGR α and 94 kDa for hGR β). In contrast to hGR α , the β isoform does not bind ligand and is unable to *trans*-activate glucocorticoid-responsive genes.

All the members of the nuclear receptor superfamily have similar 'modular' structures containing three functional domains: the N-terminal domain ('immunogenic' domain), the central 'DNA-binding domain' and the C-terminal 'ligand-binding domain'. The immunogenic domain contains a *trans*-activation domain (AF-1 or τ 1), which is important for regulation of target gene expression⁷⁻⁹. The DNA-binding domain^{7,10,11} includes a cysteine-rich region with two highly conserved 'zinc fingers' crucial for interaction with GREs, and has sequences necessary for receptor dimerization¹², nuclear translocation (NLS1)¹³ and GRE-mediated *trans*-activation^{8,14}. The ligand-binding domain, in addition to ligand binding, contains the domains of several other important functions^{7,15}, such as heat shock protein (hsp) binding¹⁶⁻¹⁸, nuclear translocation (NLS2)¹³, receptor dimerization¹⁹ and *trans*-activation function (AF-2 or τ 2)²⁰⁻²³, as well as domains for silencing of the receptor in the absence of the hormone^{8,24}. The two *trans*-activation domains interact with other nuclear proteins, the coactivators, important for stabilization and activation of the transcription initiation complex in the promoters of glucocorticoid-responsive genes.

• Intracellular Localization

Because of its ligand-binding properties and strong transcriptional activities, hGR α has been a primary focus of research for many years; hGR β in



trends in Endocrinology and Metabolism

Figure 1. Structure of the gene encoding the human glucocorticoid receptor (hGR) and gene products. Alternative splicing events (1; default splicing pathway) and (2; alternative splicing pathway) generate two different hGR messages, which differ in size owing to the use of alternative polyadenylation signals. Translation of the messages produces two isoforms of the glucocorticoid receptor, hGR α and hGR β , respectively, which have an identical structure up to amino acid 727 but then diverge. hGR α , 777 amino acids long, has a molecular mass of ~98 kDa, whereas hGR β , 742 amino acids long, has a molecular mass of ~94 kDa. Functional domains and the putative sites are indicated below the linearized GR protein. Boxes and lines represent exons and introns, respectively.

contrast, was initially discarded as an artifact, and studied only recently, when specific antibodies against the protein were generated^{25,26}. The intracellular localization of hGR β is uncertain; de Castro *et al.*²⁵ reported that, in the absence of dexamethasone, most hGR α and hGR β immunoreactivity of HeLa cells was in the cytosolic fraction, whereas incubation with dexamethasone resulted in a visible increase of the immunoreactivity of both isoforms in the nuclear fraction. In this study, the authors provided further evidence that, like hGR α , hGR β was part of a

cytosolic hetero-oligomer that contained hsp90, and that hGR β probably heterodimerizes with hGR α . By contrast, Oakley *et al.*²⁶ demonstrated that hGR β resided primarily in the nucleus of transfected cells, independently of hormone treatment, which cannot readily be explained, because hGR β has the amino acid sequences that are necessary to bind to hsp90 (Ref. 16). However, others showed that the affinity of hGR β for hsp90 was less than that of hGR α , which could explain its nuclear localization under certain conditions (J.A. Cidlowski, pers. commun.).

Recently, we also found transfected green-fluorescent protein-GR β fusion hybrid in the nucleus of transfected HeLa cells (T. Kino, unpublished). Although the import of this protein into the nucleus was extremely rapid and ligand independent, its export from the nucleus was greatly delayed when compared with the export of the green-fluorescent protein-GR α hybrid. This suggests that hGR β can accumulate in the nucleus at high concentrations, even if its translation rate is significantly lower than that of hGR α .

• Expression and Synthesis

mRNA

mRNA encoding hGR β is expressed widely in the body. In an earlier study by Bamberger *et al.*, mRNA encoding hGR β was found in several tissues, including total brain, brain cortex, amygdala, hippocampus, hypothalamus, pituitary, bone marrow, thymus, spleen, peripheral blood leukocytes, liver, kidney, lung, abdominal fat, skeletal muscle, placenta (term) and fetal lung²⁷. These findings were confirmed by Oakley *et al.*, who found mRNA transcripts in various human adult and fetal tissues and in several transformed human cell lines²⁶. Within tissues, hGR β was found at high levels in a cell type-specific manner. In particular, immunohistochemical analysis revealed that epithelial cells lining the terminal bronchiole of the lung, forming the outer layer of Hassall's corpuscle in the thymus and lining the bile duct in the liver, had high levels of hGR β . By contrast, thymic lymphocytes and other epithelial cells in these tissues showed very little immunoreactivity; moderate immunoreactivity was seen in hepatocytes²⁸.

In three independent studies of mRNA levels for GR isoforms, measured by quantitative RT-PCR, the α isoform was dominant. In the pituitary, both in adrenocorticotropin (ACTH)-secreting adenoma tissues and in non-adenomatous samples, a 30–40-fold excess of mRNA encoding hGR α was found compared with that encoding the hGR β isoform. Furthermore, although both pituitary and ectopic ACTH-secreting tumors are at least partially

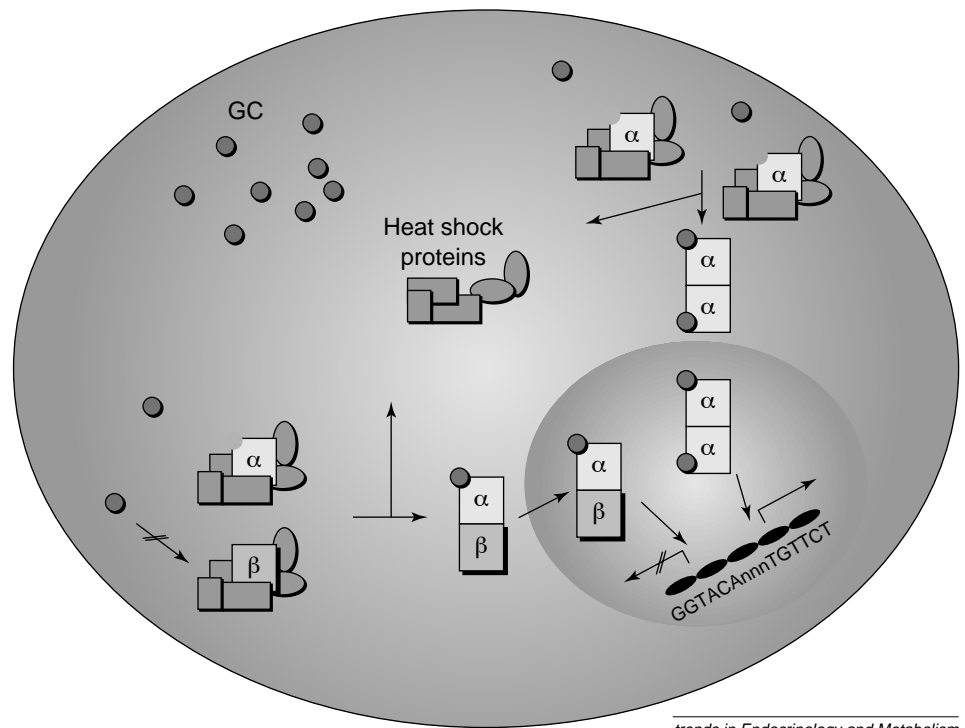
glucocorticoid resistant, no significant abnormalities in the relative expression of the mRNAs of the two isoforms were seen in a series of such tumors^{29,30}. Oakley *et al.* found 200–500 times more mRNA encoding hGR α than hGR β in a variety of tissues and cells, including human lung and liver, and HeLa-S3 and CEM-C7 cells²⁶. Finally, analysis by RT-PCR showed no evidence of the existence of mRNA encoding GR β in mice³¹.

Protein

Because mRNA transcripts encoding hGR β have been detected in many human tissues, the importance of knowing whether the protein is synthesized and at what relative concentrations led several laboratories to develop hGR β -specific antibodies^{25,28,32}. Although it was found that hGR β was synthesized in all tissues examined, the quantitative data have been controversial and need to be confirmed. Oakley *et al.* reported that the hGR β protein was found in HeLa-S3 and CEM-C7 cells, but at considerably lower concentrations than the hGR α (Ref. 28). On the other hand, de Castro *et al.* reported levels of hGR β in HeLa cells fivefold higher than those of hGR α (Ref. 25). In the only quantitative survey of human tissues, de Castro *et al.* described ratios of hGR α to hGR β ranging from 1:1 to 1:5 (Ref. 25). The latter survey used immunogenic peptides conjugated to bovine serum albumin as standards for both isoforms. When hGR α peptide immunoreactivity was compared with the immunoreactivity of known quantities of purified mouse GR α , the results were similar, with an accuracy error of up to 20%. Interestingly, the calculated quantities of hGR α immunoreactivity were significantly higher than the quantities extrapolated from ³H-dexamethasone-binding studies, suggesting that only a proportion of hGR α in a cell may be available for binding to glucocorticoids.

• Mechanisms of Action

After binding the hormone, in its new conformation, hGR α translocates into the nucleus, where it directly influences the transcription of glucocorticoid-responsive genes by binding as a



trends in Endocrinology and Metabolism

Figure 2. Putative mechanisms of action of the human glucocorticoid (GC) receptor (hGR) α and β isoforms. In the unliganded state, the classic hGR α resides predominantly in the cytoplasm as part of a heteromeric complex including at least five molecules of heat shock proteins (hsp). Hormone binding leads to a conformational change in the hGR α molecule, which allows it to dissociate from the hsp complex, homodimerize with another hormone-activated receptor molecule and translocate to the cell nucleus, where it can regulate the transcriptional activity of target genes. This can occur as a result of binding to GC-responsive elements (GREs) or through protein-protein interaction with other transcription factors. hGR β is unable to bind GCs and is transcriptionally inactive, but might have a cell-specific dominant negative effect on hGR α for GRE-mediated actions only. The GRE consensus sequence (15bp) is shown.

homodimer to specific GREs, which are present in the promoters of these genes (Fig. 2). Once bound to GREs, GR α interacts with other components of the transcription apparatus, including coactivators and corepressors, either to enhance or repress the expression of glucocorticoid-responsive genes^{33–35}.

There is a consensus that hGR β does not bind glucocorticoids or antiglucocorticoids *in vitro* and is transcriptionally inactive on a GRE-containing enhancer^{3,7,26,36–38}. In addition, hGR β was shown to bind to GRE-containing DNA oligonucleotides in a specific fashion²⁷. However, it is still not clear whether or not hGR β can exert a specific dominant negative effect on transcriptional activation induced by hGR α . Bamberger *et al.*²⁷ showed that increased production (at least fivefold) of hGR β compared with hGR α could

disrupt the enhancing effects of hGR α on a mouse mammary tumor virus (MMTV)-luciferase construct in COS-7 cells. In accordance with these findings, Oakley *et al.*²⁶ also demonstrated hGR β dominant negative activity in HeLa-S3 cells that have endogenous hGR α receptors, also in a GRE-mediated manner. Similar activity was reported in COS-7 and HeLa cells (I.J. Brogan, unpublished); furthermore, excess of hGR β was reported to repress transactivation induced by the mineralocorticoid receptor (MR)³⁹. Recently, C.A. Longui *et al.* (pers. commun.) demonstrated increased apoptosis of glucocorticoid-sensitive human leukemic cells by the addition of neutralizing complementary oligonucleotides that interfered with the synthesis of the β isoform.

Potential mechanisms responsible for this dominant negative effect

exerted by hGR β have not been elucidated yet. They might involve competition between hGR α and hGR β for GRE binding, formation of transcriptionally inactive or partially active hGR α -hGR β or MR-hGR β heterodimers, and/or competition for stoichiometrically limited concentrations of coactivators needed by hGR α for full transcriptional activity. The latter mechanism or 'squenching' has been shown to be physiologically important in several systems, including the very important interaction between hGR α and NF- κ B (Ref. 40). Interestingly, the GR β isoform has no detectable effect on AP-1- or NF- κ B-mediated actions in COS-7, HEK-293, HeLa or Jurkat cells^{41,42} and, hence, its presence in a cell would preferentially influence GRE-mediated actions.

Carlstedt-Duke's group³² found no evidence for a specific dominant negative effect of GR β on *trans*-activation induced by hGR α . Similarly, Brogan *et al.* found that hGR β did not repress hGR α -dependent *trans*-activation in HEK-293 embryonic kidney cells (I.J. Brogan, unpublished). Furthermore, cotransfection of hGR β in primary human lymphocytes or Jurkat T lymphoma cells had no effect on *trans*-activation by the hGR α isoform, even when the hGR β protein was found at more than five times higher levels than hGR α (Ref. 42).

These discrepant results could be explained by the use of different vectors, cell/tissue-specificity or problems connected to the transient transfection systems used. However, it is noteworthy that we and others have used the same transfection system in the evaluation of our patients with genetic forms of generalized glucocorticoid resistance and have found that it has reflected appropriately the functional defect and the clinical picture of the patients^{36-38,43}.

• Glucocorticoid Sensitivity

Many studies have demonstrated in a variety of systems that there is a direct correlation between the concentration of the GR in a cell and the cell's sensitivity to glucocorticoids⁴⁴⁻⁴⁷. Genetic abnormalities of the GR – primarily

inactivating mutations of the ligand-binding domain or mutations leading to functional knockout of one of the two GR gene alleles – have been described³⁷. These mutations lead to generalized glucocorticoid resistance compensated for by hyperactivity of the hypothalamic-pituitary-adrenal axis. The excessive ACTH, cortisol, cortisol precursors with mineralocorticoid activity (primarily DOC and corticosterone) and adrenal androgens (primarily androstenedione) produce pathology in many of these subjects, mainly hypertension with or without hypokalemic alkalosis and the entire range of hyperandrogenism in women and children.

A pathological dominant negative hGR mutant with substitution of isoleucine for asparagine at position 559 of the protein was described recently. This receptor had a three- to fourfold higher dominant negative activity than hGR β in the same MMTV-luciferase assay, and was found at a 1:1 ratio with normal hGR α in the patient's cells. This patient had marked glucocorticoid resistance leading to an approximately five- to tenfold elevation of his urinary free cortisol levels⁴³.

A genetically determined imbalance of the glucocorticoid receptor isoforms was found recently in cultured lymphocytes from a patient with congenital generalized glucocorticoid resistance and chronic leukemia; this patient presented with greatly reduced hGR α and normal hGR β levels, resulting in a low hGR α to hGR β ratio⁴⁸. There was no abnormality in the sequence of the entire cDNA and individual exons of the gene encoding hGR in this patient; however, the low hGR α concentration could explain the glucocorticoid resistance of this patient.

Glucocorticoids are used widely for the suppression of inflammation in chronic autoimmune/inflammatory and allergic diseases, such as rheumatoid arthritis, inflammatory bowel disease and asthma, as well as for suppression of lymphoid tissue in lymphoproliferative neoplasms, such as lymphoma or leukemia, and other conditions. Indeed, glucocorticoids are often the most effective therapy available; however, their use in some

patients is hampered by systemic side effects.

A proportion of patients with autoimmune/inflammatory or allergic diseases treated with glucocorticoids requires or fails to respond to high doses of those hormones. This is immune system-specific glucocorticoid resistance and appears to be the result of tissue-specific defects of the GR transduction system. This condition might be genetically/constitutionally determined and/or acquired and has been studied extensively in asthma⁴⁹⁻⁵¹ and less extensively in other inflammatory diseases, including rheumatoid arthritis⁵² and inflammatory bowel disease^{53,54}. There might be several mechanisms responsible for this phenomenon, including changes in intracellular hormone availability, levels of cellular hGR α , hormone-binding affinity, hormone-induced conformational change and dissociation from the hsp complex. Other mechanisms could involve phosphorylation, nuclear translocation, GRE binding and/or interaction with other nuclear factors, as well as abnormally high levels of hGR β .

Indeed, in glucocorticoid-resistant asthma type 1 patients, significantly higher numbers of hGR β immunoreactive cells were found in the peripheral blood of glucocorticoid-sensitive asthmatics than in normal controls⁵⁵. Similar data were found when bronchial lavage cells from patients with steroid-resistant and -sensitive asthma were investigated, with higher numbers of hGR β immunoreactive cells in resistant than in sensitive cells. The synthesis of hGR β was cytokine-inducible [interleukin 2 (IL-2) and IL-4] in peripheral blood leukocytes from normal subjects, but reverted to normal levels when glucocorticoid-resistant cells were incubated in the absence of cytokines⁵⁵. This finding suggested that cytokine-induced synthesis of hGR β might be involved directly in the development of glucocorticoid insensitivity in certain patients with chronic asthma. In patients with the rarer glucocorticoid-resistant asthma type 2, a genetically determined non-reversible decrease of the hGR α to hGR β ratio could be responsible for glucocorticoid resistance of the immune cells.

Animal models of systemic glucocorticoid resistance, such as New World primates, including squirrel, marmoset and owl monkeys, might also have increased relative synthesis of the β isoform of the GR. These animals have total plasma cortisol levels that are 7–20 times higher than in humans or other Old World primates⁵⁶, whereas the concentration, affinity and predicted amino acid sequence of their GRs are similar to those of the human receptor⁵⁷. Furthermore, these animals exhibit resistance to a variety of other hormones, including estrogens, progesterone, androgens, aldosterone and vitamin D (Refs 58–60). Immunoreactivity of both isoforms of the GR has been found in Epstein–Barr virus-transformed B lymphocytes from marmosets, with the β isoform being approximately ten times overproduced compared with the corresponding human cells (M. de Castro, unpublished). An altered splicing pattern of GR pre-mRNA or differential mRNA translation or degradation and/or GR protein degradation rates might contribute to the steroid resistance of these animals. Alternatively, these animals might have decreased activity of coactivators and/or increased activity of corepressors, leading to ‘pansteroid’ resistance.

• Conclusions

Glucocorticoids are essential for life and their actions are important for maintaining basal and stress-related homeostasis. Glucocorticoid effects are exerted via the ligand-binding hGR α ; the non-ligand-binding isoform hGR β might have mild, fine-tuning negative effects, pertaining primarily to GRE-mediated actions of GR α ; that is, primarily activational and metabolic effects, and possibly apoptosis in a select type of cell or tissue. These effects might be specific, by direct interactions with hGR α and GREs, or nonspecific, as a result of squelching of transcription cofactors that are important for glucocorticoid-modulated transcription, but are present in limited quantities. hGR β has been shown to bind to hsp90, to translocate into and accumulate in the nucleus (and, hence, to have at least one active nuclear localization signal) and to be exported from the

nucleus at an extremely slow rate. hGR β also has intact AF-1 and AF-2 sequences, which might interact with nuclear receptor coregulators in competition with hGR α . More work is needed to determine the involvement of hGR β in human physiology and pathophysiology.

References

- Munck, A. and Leung, K. (1997) **Glucocorticoid receptors and mechanisms of action.** In *Receptors and Mechanism of Action of Steroid Hormones* (2nd edn) (Pasqualini, J.R., ed.), pp 311–329, Marcel Dekker
- Fuller, P.J. (1991) **The steroid receptor superfamily: mechanisms of diversity.** *FASEB J.* 5, 3092–3099
- Hollenberg, S.M. *et al.* (1985) **Primary structure and expression of a functional human glucocorticoid receptor cDNA.** *Nature* 318, 635–641
- Encio, I.J. and Detera-Wadleigh, S.D. (1991) **The genomic structure of the human glucocorticoid receptor.** *J. Biol. Chem.* 266, 7182–7188
- Evans, R.M. (1988) **The steroid and thyroid hormone receptor superfamily.** *Science* 240, 889–895
- Mangelsdorf, D.J. *et al.* (1995) **The nuclear receptor superfamily: the second decade.** *Cell* 83, 835–839
- Giguere, V., Hollenberg, S.M., Rosenfeld, M.G. and Evans, R.M. (1986) **Functional domains of the human glucocorticoid receptor.** *Cell* 46, 645–652
- Hollenberg, S.M., Giguere, V., Segui, P. and Evans, R.M. (1987) **Colocalization of DNA-binding and transcriptional activation functions in the human glucocorticoid receptor.** *Cell* 49, 39–46
- Dahlman-Wright, K., Almlof, T., McEwan, I.J., Gustafsson, J.A. and Wright, A.P. (1994) **Delineation of a small region within the major transactivation domain of the human glucocorticoid receptor that mediates transactivation of gene expression.** *Proc. Natl. Acad. Sci. U. S. A.* 91, 1619–1623
- Freedman, L.P. *et al.* (1988) **The function and structure of the metal coordination sites within the glucocorticoid receptor DNA binding domain.** *Nature* 334, 543–546
- Zilliagus, J., Wright, A.P., Carlstedt-Duke, J. and Gustafsson, J.A. (1995) **Structural determinants of DNA-binding specificity by steroid receptors.** *Mol. Endocrinol.* 9, 389–400
- Tsai, S.Y. *et al.* (1988) **Molecular interactions of steroid hormone receptor with its enhancer element: evidence for receptor dimer formation.** *Cell* 55, 361–369
- Picard, D. and Yamamoto, K.R. (1987) **Two signals mediate hormone-dependent nuclear localization of the glucocorticoid receptor.** *EMBO J.* 6, 3333–3340
- Lefstin, J.A., Thomas, J.R. and Yamamoto, K.R. (1994) **Influence of a steroid receptor DNA-binding domain on transcriptional regulatory functions.** *Genes Dev.* 8, 2842–2856
- Warriar, N., Yu, C. and Govindan, M.V. (1994) **Hormone binding domain of human glucocorticoid receptor. Enhancement of transactivation function by substitution mutants M565R and A573Q.** *J. Biol. Chem.* 269, 29010–29015
- Dalman, F.C., Scherrer, L.C., Taylor, L.P., Akil, H. and Pratt, W.B. (1991) **Localization of the 90-kDa heat shock protein-binding site within the hormone-binding domain of the glucocorticoid receptor by peptide competition.** *J. Biol. Chem.* 266, 3482–3490
- Hutchison, K.A. *et al.* (1993) **Regulation of glucocorticoid receptor function through assembly of a receptor–heat shock protein complex.** *Ann. New York Acad. Sci.* 684, 35–48
- Pratt, W.B. (1993) **The role of heat shock proteins in regulating the function, folding, and trafficking of the glucocorticoid receptor.** *J. Biol. Chem.* 268, 21455–21458
- Dahlman-Wright, K., Wright, A.P. and Gustafsson, J.A. (1992) **Determinants of high-affinity DNA binding by the glucocorticoid receptor: evaluation of receptor domains outside the DNA-binding domain.** *Biochemistry* 31, 9040–9044
- Hollenberg, S.M. and Evans, R.M. (1988) **Multiple and cooperative trans-activation domains of the human glucocorticoid receptor.** *Cell* 55, 899–906
- Webster, N.J., Green, S., Jin, J.R. and Chambon, P. (1988) **The hormone-binding domains of the estrogen and glucocorticoid receptors contain an inducible transcription activation function.** *Cell* 54, 199–207
- Danielian, P.S., White, R., Lees, J.A. and Parker, M.G. (1992) **Identification of a conserved region required for hormone dependent transcriptional activation by steroid hormone receptors [published erratum appears in EMBO J. (1992) 11, 2366].** *EMBO J.* 11, 1025–1033
- Lanz, R.B. and Rusconi, S. (1994) **A conserved carboxy-terminal subdomain is important for ligand interpretation and transactivation by nuclear receptors.** *Endocrinology* 135, 2183–2195
- Godowski, P.J., Rusconi, S., Miesfeld, R. and Yamamoto, K.R. (1987) **Glucocorticoid receptor mutants that are constitutive activators of transcriptional enhancement [published erratum appears in Nature (1987) 326, 105].** *Nature* 325, 365–368
- de Castro, M. *et al.* (1996) **The non-ligand binding beta-isoform of the human glucocorticoid receptor (hGR beta): tissue levels, mechanism of action, and potential physiologic role.** *Mol. Med.* 2, 597–607
- Oakley, R.H., Sar, M. and Cidlowski, J.A. (1996) **The human glucocorticoid receptor beta isoform. Expression, biochemical properties, and putative function.** *J. Biol. Chem.* 271, 9550–9559
- Bamberger, C.M., Bamberger, A.M., de Castro, M. and Chrousos, G.P. (1995) **Glucocorticoid receptor beta, a potential endogenous inhibitor of glucocorticoid action in humans.** *J. Clin. Invest.* 95, 2435–2441

- 28 Oakley, R.H., Webster, J.C., Sar, M., Parker, C.R.J. and Cidlowski, J.A. (1997) **Expression and subcellular distribution of the beta-isoform of the human glucocorticoid receptor.** *Endocrinology* 138, 5028–5038
- 29 Mu, Y.M. *et al.* (1998) **Low level of glucocorticoid receptor messenger ribonucleic acid in pituitary adenomas manifesting Cushing's disease with resistance to a high dose-dexamethasone suppression test.** *Clin. Endocrinol.* 49, 301–306
- 30 Dahia, P.L. *et al.* (1997) **Expression of glucocorticoid receptor gene isoforms in corticotropin-secreting tumors.** *J. Clin. Endocrinol. Metab.* 82, 1088–1093
- 31 Otto, C., Reichardt, H.M. and Schütz, G. (1997) **Absence of glucocorticoid receptor-beta in mice.** *J. Biol. Chem.* 272, 26665–26668
- 32 Hecht, K. *et al.* (1997) **Evidence that the beta-isoform of the human glucocorticoid receptor does not act as a physiologically significant repressor.** *J. Biol. Chem.* 272, 26659–26664
- 33 Yamamoto, K.R. (1985) **Steroid receptor regulated transcription of specific genes and gene networks.** *Annu. Rev. Genet.* 19, 209–252
- 34 Burnstein, K.L. and Cidlowski, J.A. (1989) **Regulation of gene expression by glucocorticoids.** *Annu. Rev. Physiol.* 51, 683–699
- 35 Beato, M. (1989) **Gene regulation by steroid hormones.** *Cell* 56, 335–344
- 36 Hurley, D.M. *et al.* (1991) **Point mutation causing a single amino acid substitution in the hormone binding domain of the glucocorticoid receptor in familial glucocorticoid resistance.** *J. Clin. Invest.* 87, 680–686
- 37 Chrousos, G.P., Detera-Wadleigh, S.D. and Karl, M. (1993) **Syndromes of glucocorticoid resistance.** *Ann. Intern. Med.* 119, 1113–1124
- 38 Karl, M. *et al.* (1993) **Familial glucocorticoid resistance caused by a splice site deletion in the human glucocorticoid receptor gene.** *J. Clin. Endocrinol. Metab.* 76, 683–689
- 39 Bamberger, C.M., Bamberger, A.M., Wald, M., Chrousos, G.P. and Schulte, H.M. (1997) **Inhibition of mineralocorticoid activity by the beta-isoform of the human glucocorticoid receptor.** *J. Steroid Biochem. Mol. Biol.* 60, 43–50
- 40 Sheppard, K.A. *et al.* (1998) **Nuclear integration of glucocorticoid receptor and nuclear factor-kappaB signaling by CREB-binding protein and steroid receptor coactivator-1.** *J. Biol. Chem.* 273, 29291–29294
- 41 de Lange, P. *et al.* (1997) **Differential hormone-dependent transcriptional activation and repression by naturally occurring human glucocorticoid receptor variants.** *Mol. Endocrinol.* 11, 1156–1164
- 42 Bamberger, C.M., Else, T., Bamberger, A.M., Beil, F.U. and Schulte, H.M. (1997) **Regulation of the human interleukin-2 gene by the alpha and beta isoforms of the glucocorticoid receptor.** *Mol. Cell. Endocrinol.* 136, 23–28
- 43 Karl, M. *et al.* (1996) **Cushing's disease preceded by generalized glucocorticoid resistance: clinical consequences of a novel, dominant-negative glucocorticoid receptor mutation.** *Proc. Assoc. Amer. Physic.* 108, 296–307
- 44 Bourgeois, S. and Newby, R.F. (1979) **Correlation between glucocorticoid receptor and cytolytic response of murine lymphoid cell lines.** *Cancer Res.* 39, 4749–4751
- 45 Danielsen, M. and Stallcup, M.R. (1984) **Down-regulation of glucocorticoid receptors in mouse lymphoma cell variants.** *Mol. Cell. Biol.* 4, 449–453
- 46 Gehring, U., Mugele, K. and Ulrich, J. (1984) **Cellular receptor levels and glucocorticoid responsiveness of lymphoma cells.** *Mol. Cell. Endocrinol.* 36, 107–113
- 47 Vanderbilt, J.N., Miesfeld, R., Maler, B.A. and Yamamoto, K.R. (1987) **Intracellular receptor concentration limits glucocorticoid-dependent enhancer activity.** *Mol. Endocrinol.* 1, 68–74
- 48 Shahidi, H. *et al.* (1999) **Imbalanced expression of the glucocorticoid receptor isoforms in cultured lymphocytes from a patient with systemic glucocorticoid resistance and chronic lymphocytic leukemia.** *Biochem. Biophys. Res. Commun.* 254, 559–565
- 49 Barnes, P.J. and Adcock, I.M. (1995) **Steroid resistance in asthma.** *Q. J. Med.* 88, 455–468
- 50 Barnes, P.J., Greening, A.P. and Crompton, G.K. (1995) **Glucocorticoid resistance in asthma.** *Am. J. Respir. Crit. Care Med.* 152, S125–S140
- 51 Szeffer, S.J. and Leung, D.Y. (1997) **Glucocorticoid-resistant asthma: pathogenesis and clinical implications for management.** *Eur. Respir. J.* 10, 1640–1647
- 52 Kirkham, B.W., Corkill, M.M., Davison, S.C. and Panayi, G.S. (1991) **Response to glucocorticoid treatment in rheumatoid arthritis: *in vitro* cell mediated immune assay predicts *in vivo* responses.** *J. Rheumatol.* 18, 821–825
- 53 Franchimont, D.P., Louis, E., Croes, F. and Belaiche, J. (1998) **Clinical pattern of corticosteroid dependent Crohn's disease.** *Eur. J. Gastroenterol. Hepatol.* 10, 821–825
- 54 Franchimont, D. *et al.* (1999) **Decreased corticosteroid sensitivity in quiescent Crohn's disease. An *ex vivo* study using whole blood cell culture.** *Dig. Dis. Sci.* 44, 1208–1215
- 55 Leung, D.M. *et al.* (1997) **Association of glucocorticoid insensitivity with increased expression of glucocorticoid receptor beta.** *J. Exp. Med.* 186, 1567–1574
- 56 Chrousos, G.P. *et al.* (1982) **Glucocorticoid hormone resistance during primate evolution: receptor-mediated mechanisms.** *Proc. Natl. Acad. Sci. U. S. A.* 79, 2036–2040
- 57 Brandon, D.D. *et al.* (1991) **Genetic variation of the glucocorticoid receptor from a steroid-resistant primate.** *J. Mol. Endocrinol.* 7, 89–96
- 58 Chrousos, G.P., Loriaux, D.L. and Lipsett, M.B. (1986) *Steroid hormone resistance.* *Adv. Exp. Med. Biol.* (Vol. 196) (Chrousos, G.P., Loriaux, D.L., and Lipsett, M.B., eds), Plenum Press
- 59 Chrousos, G.P. *et al.* (1984) **Uterine estrogen and progesterone receptors in an estrogen- and progesterone-resistant primate.** *J. Clin. Endocrinol. Metab.* 58, 516–520
- 60 Gacad, M.A. and Adams, J.S. (1991) **Endogenous blockade of 1,25-dihydroxyvitamin D-receptor binding in New World primate cells.** *J. Clin. Invest.* 87, 996–1001

Correspondence

TEM encourages comment on all published articles. Letters to the Editor should be addressed to:

Trends in Endocrinology and Metabolism
68 Hills Road, Cambridge, UK CB2 1LA

Tel: +44 1223 315961
Fax: +44 1223 464430
e-mail: tem@current-trends.com