MEDICAL GRAND ROUNDS

"DISORDERS OF STEROID AND THYROID HORMONE RECEPTORS"

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INTRODUCTION

The focus of endocrinology has largely been on hormones themselves, and most disorders of clinical endocrinology result either from hormone deficiency or hormone excess. Indeed, for at least 75 years endocrinology developed without any insight into the mechanism of action of hormones. Endocrinology, basic and clinical, was changed by the description in one patient of the syndrome of pseudohypoparathyroidism by Fuller Albright and his colleagues in 1942 (1). This paper demonstrated the existence of a third type of endocrine disease in which the defect resides neither in hormone deficit nor hormone excess but in the capacity of the tissues to respond to the hormone - so-called hormone resistance. Shortly thereafter it was established that resistance to hormone action is the cause of the syndrome of testicular feminization, now believed to be the most common form of primary hormone resistance (2, 3). This conceptual breakthrough has had far-reaching effects for endocrinology. First, more and more disorders have been recognized in man and in animals in which disease results from resistance to hormone action. Second, the study of the various hormone resistance states has provided major insight into how hormones act within target cells. Each patient or animal with hormone resistance is a natural laboratory for investigating the mechanism of hormone action. Third, recognition that a disorder is due to hormone resistance has important therapeutic implications. To design rational therapy for such disorders it is necessary to know the exact site in metabolism at which the basic defect occurs.

Individuals with true hormone resistance are insensitive to both endogenous and exogenous hormones; such resistance can arise from a variety of etiologies including physiological antagonism, as in the insulin insensitivity of acromegaly, development of antibodies that block hormones or hormone receptors, as in myasthenia gravis, primary abnormalities of hormone receptors as in pseudohypoparathyroidism, or disorders of the post-receptor effector mechanisms.

When Verhoeven and I previously reviewed the subject of primary hormone resistance, we divided the subject into those disorders involving hormones in which the primary receptor mechanism is located in the cell surface and those in which the receptor is intracellular (4). In the interim so many advances have been made in understanding how hormones act that it is not practical to review both of these subjects within one hour. I therefore propose to focus this review on those syndromes involving defects in the intracellular hormone receptors of the erb A type, namely the thyroid and steroid hormone receptor superfamily. At the molecular level the defects have been defined in only a small number of patients with disorders of these receptors. It is nevertheless appropriate to review the topic because of the insight provided into hormone action - normal and abnormal. (The subject of resistance to hormones that act at the cell surface will have to be reserved for a later discussion.)

Although resistance to adrenal steroids is relatively infrequent, more is known about the action of glucocorticoids than that of any other hormone. Furthermore, since all steroids and thyroid hormones probably act by fundamentally similar mechanisms, I will begin with a consideration of the current concepts of adrenal steroid action and the syndromes in which that action is impaired. The action - normal and impaired - of androgens, vitamin D, thyroid hormones, progesterone, and estradiol will then be considered.

THE STEROID AND THYROID HORMONE RECEPTOR SUPERFAMILY

Beginning in the early 1900's three major classes of steroid hormones were delineated on the basis of biological assays and chemical characterization - the adrenal steroids (glucocorticoids and mineralocorticoids), the gonadal steroids (estrogen, androgen, and progesterone), and vitamin D. The problem was how to explain how such small molecules can have widespread and diverse effects throughout the body. When radiolabeled hormones of high specific activity became available in the 1960's it was soon established that each of these hormones (and thyroid hormones) interact with specific intracellular receptor proteins and that in each case the hormone causes a change in the receptor so that the hormone-receptor complex binds to chromosomes. This chromosome interaction in turn leads to the induction or repression of a limited number of genes (50 to 100 per cell). Selectivity and specificity of action is determined in part by restricted expression of different receptors in different cells and in part by the fact that chromosomal structure of each cell type is uniquely organized so that different sets of genes are accessible to the hormone-receptor complex (5).

Attempts to purify these receptor proteins by the classical approach of protein chemistry were complicated by the fact that they are trace proteins that have to be purified 100,000 to a million fold to achieve purity and by the fact that they are inherently not very stable, but by the early 1980's the glucocorticoid, estrogen, thyroid, and vitamin D receptors had been purified to near homogeneity (6, 7). The glucocorticoid receptor, for example, was purified by a combination of photoaffinity labeling and electrophoresis, and limited proteolysis with trypsin and chymotrypsin of crude and purified receptor revealed three functional domains of the molecule - namely a steroid hormone binding domain, a DNA binding domain, and an immunodominant domain (8). The concept of functional domains was confirmed when the cDNAs for the receptors were cloned.

The cloning of the cDNA for the human glucocorticoid receptor made it possible to deduce the complete amino acid structure for the receptor (9-11). This molecule contained a segment with remarkable homology to the viral oncogene erb A. A similar relationship of the other receptors in this group to erb A was independently confirmed by the cloning of the estrogen, progesterone, aldosterone, and vitamin D receptors (5). This finding constituted a true breakthrough for it suggested a unifying hypothesis for the structure of the receptors and hence for the action of the hormones. Namely, although steroid and thyroid hormones are not structurally related, the existence of a common structure for their receptors suggests that there is a large superfamily of genes whose products are ligand-responsive transcription factors. [One consequence of this formulation has been to search for other receptors by means of hybridization techniques; this subject is beyond the scope of this discussion but has already led to the discovery of several mammalian receptors whose ligands are not identified, to a second type of thyroid hormone receptor, to the receptor for vitamin A acid, and to a number of candidate receptor proteins in invertebrates (5).]

As stated above, the division of the structure of the glucocorticoid receptors into three functional domains that had been deduced from proteolysis of the mouse glucocorticoid receptor was confirmed by studies of the cloned cDNA

for the protein and subsequently was shown to be applicable to the other receptors of this class as well.

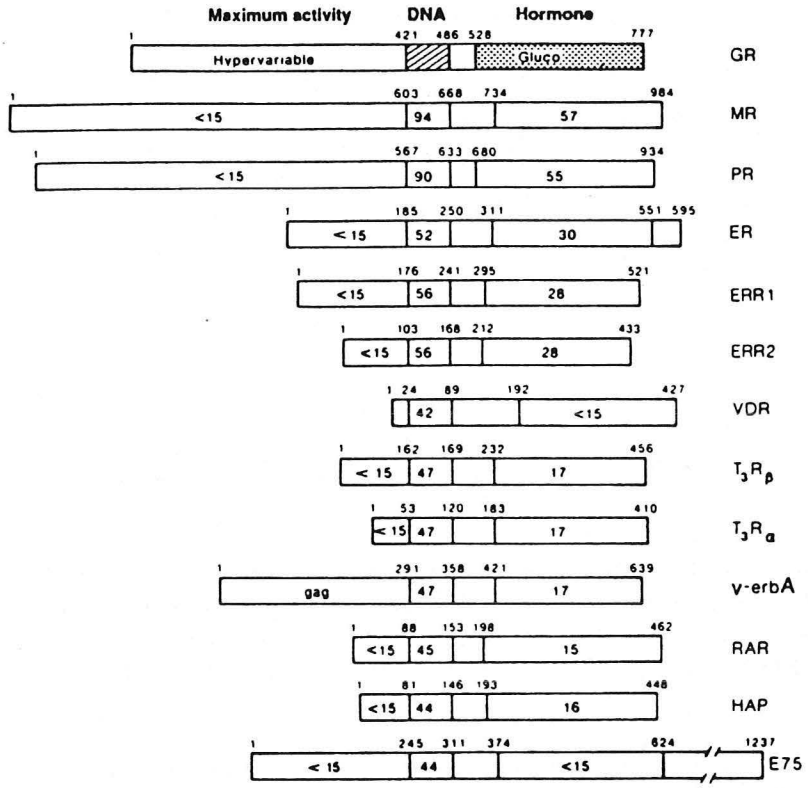


Figure 1. Schematic comparison of the amino acid compositions for several members of the steroid-thyroid receptor superfamily (5).

While the various receptors vary considerably in molecular weight they each contain a hormone binding region, a DNA binding region, and the so-called immunodominant or functional domain. The best understood of these regions is the DNA binding region (5). Of 65 residues 20 are invariant among the various receptors, 7 additional residues are conserved in most, and more than half are conserved in a majority. Nine of the invariant residues are cystines, and one invariant residue is histidine. This motif had already been described in another transcription factor and was known to allow the folding of the protein into so-called fingers or loops coordinated by a zinc ion. These fingers of amino acids are believed to interact with a half turn of DNA.

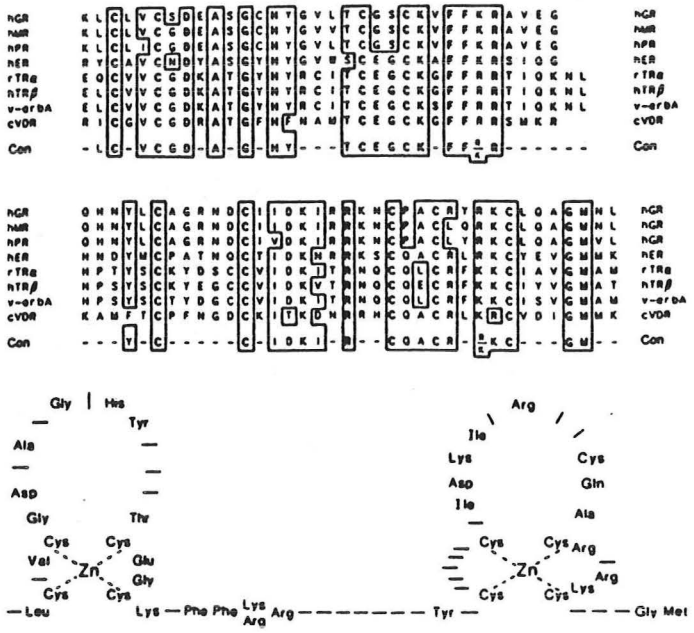


Figure 2. Amino acid sequence comparison of DNA-binding domains for several receptors (top). The bottom shows the hypothetical structure of the DNA-binding domains for these receptors (5).

The initial suspicion that the DNA binding domain was in the most highly conserved central core of the protein was proven by substituting this region of the human estrogen receptor with that of the human glucocorticoid receptor; under this circumstance glucocorticoid acted like an estrogen (13).

Site-directed mutagenesis has confirmed that the conserved residues and the zinc are both essential for binding of the receptor-hormone complex to DNA (12). [The first human disease due to a mutation in this region involves the vitamin D receptor (see below).] The fingers are encoded by separate exons, and the amino terminal of the two fingers is more highly conserved than the more carboxy terminal one.

The definition of the hormone-binding domain for the glucocorticoid receptor was made possible by inserting site-directed mutations of the molecule into cells coinfected with a vector containing a known glucocorticoid response element [the mouse mammary tumor virus (MMTV, see below)] attached to a reporter gene; mutations in this region impair hormone binding to the receptor and hormone action in a parallel fashion. An unexpected and revealing finding is that deletion of the hormone binding region of the glucocorticoid receptor renders the receptor constitutively active (5). This finding provided the first mechanical model of how the hormone acts.

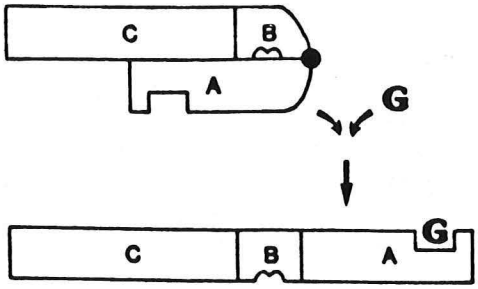


Figure 3. Model for activation of GR. After the binding of glucocorticoid (G), the complex undergoes a conformational change centered around a hinge region at the border between the steroid-binding domain (A) and the DNA-binding domain (B) (8).

Neither the steroid binding domain of the receptor nor the steroid itself is needed for DNA binding or transcription enhancement. Instead, the hormone binding domain normally prevents the domains for DNA binding and transcriptional activation from functioning. The addition of hormone relieves this inhibition probably by causing an allosteric change in receptor shape. The model shown in Figure 3 is almost certainly an oversimplification because regulation by the steroid binding domain appears to be largely independent of its site within the molecule (13A).

The amino terminal regions of the receptors vary in length and in amino acid composition. Nevertheless, the amino terminal or immunological domain is critical for function as indicated by analysis of receptors that contain mutations in this region; such receptors bind hormone normally and bind DNA normally (or better than normal) but do not function biologically. Likewise, receptors with deletions in the region can regulate some gene function but are 10-20 fold less active than the native receptor (5).

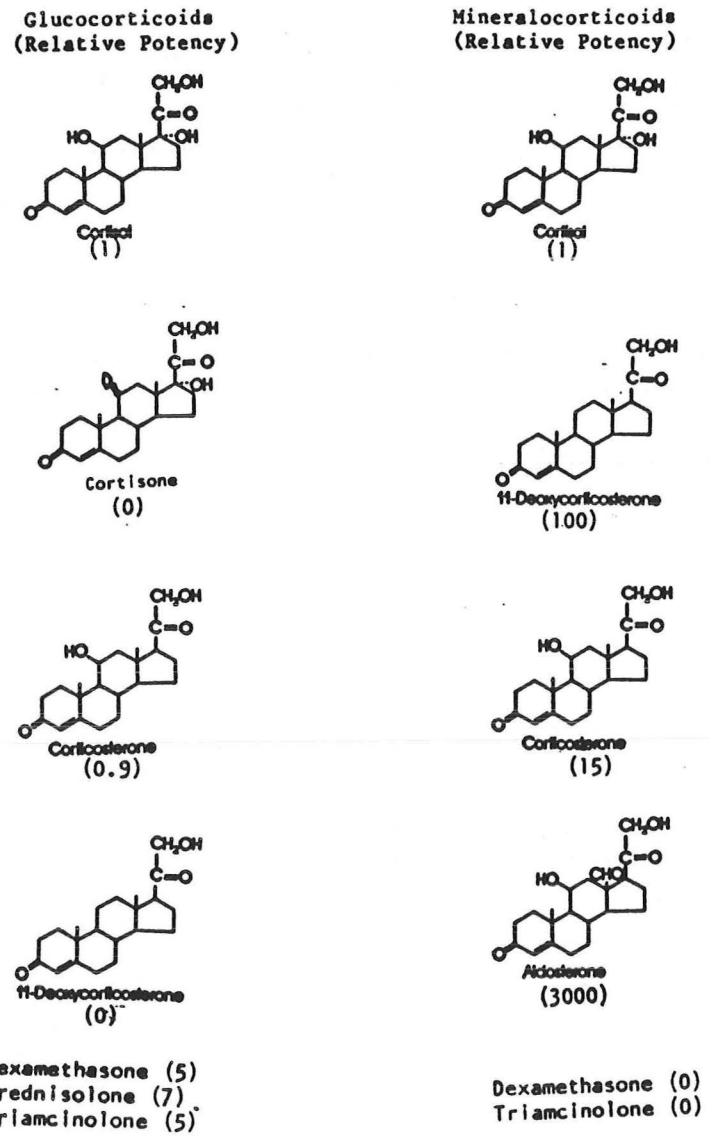
It should also be pointed out that individual hormones may have multiple receptors. In part this variability may be due to alternative processing of the genes themselves and/or differential processing of the messenger RNAs for the genes as is the case for the progesterone receptor. In addition, two separate thyroid hormone receptors are the products of separate genes, and there may be additional thyroid hormone genes. Whether these different receptors for the same hormone are critical for tissue specific hormonal effects, whether they mediate different actions of the hormone, or whether they respond differently to metabolic and/or hormonal regulation is not known. [For detailed reviews of the current concepts of the function of the erb A superfamily, including V-erb-A itself, the evolution of the system, the mechanisms of molecular interaction between the ligand the receptor, and the molecular interactions that lead to activation of transcription see reviews (5, 6, 7, 12).]

ADRENAL STEROIDS

Glucocorticoids and Mineralocorticoids

The adrenal cortex produces two principal types of steroid hormones - namely steroids with glucocorticoid or mineralocorticoid properties. Glucocorticoid signifies a C_{21} steroid with a predominant action on intermediary metabolism; mineralocorticoid indicates a C_{21} steroid with predominant action on the metabolism of sodium and potassium. The major species of these hormones are shown below.

Figure 4. Relative Potencies of Some Adrenal Steroids



The receptors for these hormones were originally identified by analyzing the binding of radiolabeled ligands - [^{3}H]dexamethasone or [^{3}H]triamcinolone - acetonide, which have high affinity for the glucocorticoid receptor, and [^{3}H]aldosterone, which binds with high affinity to receptors in the typical

mineralocorticoid target tissues. However, the problem has been that in vitro these receptors show similar binding affinities for the various ligands, namely both "glucocorticoid receptor" and "mineralocorticoid receptor" bind mineralocorticoids and glucocorticoids with similar affinities. In contrast, in intact animals whereas radioactive aldosterone is taken up and retained by glucocorticoid receptors, radioactive glucocorticoids are not bound by mineralocorticoid receptors. This confusing situation in which there is a gross discrepancy between the in vitro binding properties and the physiological actions of mineralocorticoids and glucocorticoids has been clarified by studies of the apparent mineralocorticoid excess syndrome that occurs in 11-beta-hydroxysteroid dehydrogenase deficiency (14). In this disorder hydrocortisone (and other 11-hydroxysteroids) are not oxidized to 11-keto derivatives such as cortisone. In this situation cortisol can bind to mineralocorticoid receptor in the kidney and act as a potent mineralocorticoid (15). Thus, in the normal state the receptor in mineralocorticoid target tissues are selective for aldosterone in vivo because of the presence of the enzyme 11-beta-hydroxysteroid dehydrogenase which converts glucocorticoids, but not aldosterone, to the 11-keto analogues (15). These 11-keto analogues cannot bind to mineralocorticoid receptors. The net consequence is that the action of these hormones is determined not by the structures of the hormones directly but by a combination of the properties of the receptors and of the metabolic pathways that determine which type of steroid molecule is present in individual cell types. For the purposes of this discussion glucocorticoid action is defined as actions mediated by the glucocorticoid receptor, and mineralocorticoid action is mediated by the mineralocorticoid receptor.

Glucocorticoid Action

The gene that specifies the human glucocorticoid receptor is on Chromosome 5 (8). There are between 5000 and 100,000 receptor molecules per cell depending on the cell type, and the apparent kD for cortisol is 20-40 nM, the same concentration as that of free cortisol in plasma; the net consequence is that approximately half of the receptors are occupied with glucocorticoid under physiological conditions. Following transformation of the hormone-receptor complex to the DNA-binding state approximately 50-70% of hormone-receptor complexes bind to acceptor sites within the chromatin. It is not clear exactly how many forms of the glucocorticoid receptor exist within cells. In contrast to some other receptors (such as progesterone) there either appears to be no down-regulation or incomplete down-regulation of the glucocorticoid receptor by glucocorticoids (16). Also in contrast to the estrogen and progesterone receptors, the unoccupied glucocorticoid receptor appears to be located in the cytoplasmic compartment of the cell, and the hormone-receptor complex forms in the cytosol and moves rapidly into the nuclear compartment after administration of the hormone (8). The capacity for the receptor to move to the nucleus is coded by two regions of the receptor - a 28 amino acid segment near the DNA binding domain and a 256 amino acid region that includes the hormone binding domain; fusion proteins containing either full length receptor or the 256 amino acid region alone move from cytoplasm into the nucleus but only in the presence of hormone (17).

The concept that hormone-receptor complexes act by binding with specific regulatory elements in the regions 5' to the coding sequence of hormone-responsive genes is largely based upon studies of the mouse mammary

tumor virus (MMTV) (18). This virus is a 60-70S single stranded RNA retrovirus. The DNA transcript of this virus (provirus) is integrated into the DNA of host organisms, and the virus is transcribed from the integrated viral DNA. The virus is transmitted in milk and causes a high incidence of tumors in susceptible mouse strains, but in fact provirus is present in multiple copies in all mouse strains. Glucocorticoids have a profound effect on the replication of MMTV; for example hydrocortisone causes an enormous increase in cytoplasmic inclusion bodies in such tumors, and in cultured epithelial cells carrying the virus hydrocortisone stimulates virus replication 10-20 fold above basal levels. In this system, it was first demonstrated that glucocorticoids induce the synthesis of messenger RNA within 30 minutes of administration, namely the synthesis of a single long RNA transcript that is processed into mRNAs for all the protein constituents of the virus. The virus contains long terminal repeats (LTR's) that flank the structural genes, and these LTR's contain both the promoter and the polyadenylation sites.

Five regions of the MMTV provirus bind the glucocorticoid-receptor complex - one site is upstream to the transcription start site near the promoter, and the others are within the transcribed sequence. Each of the five sites binds at least two molecules of receptor, but only the upstream receptor is glucocorticoid responsive. This region of DNA has been termed the glucocorticoid response element (GRE) or steroid response element (SRE). Glucocorticoid response elements have also been defined for other glucocorticoid responsive genes, and in the majority of cases they are 200-500 base pairs upstream from the initiation sites. A comparison of the binding sites for several steroid hormone response elements indicates a degenerative consensus sequence for glucocorticoid receptor binding: TGTTCT.

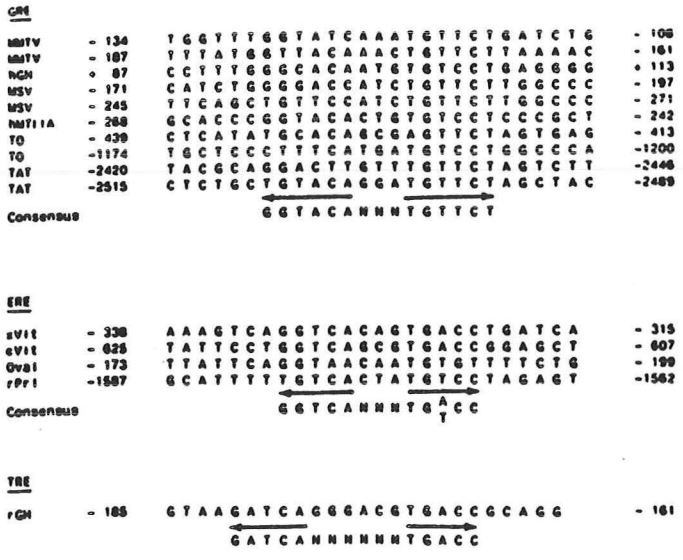


Figure 5. Alignments of the nucleic acid sequences of known hormone regulatory elements from genes that respond to glucocorticoids (GRE), estrogen (ERE) and thyroid hormone (TRE) (5).

Some of the GRE sites bind multiple hormone receptors. For example, the upstream sequence for MMTV recognizes and responds both to glucocorticoid and to progesterone receptors (19). However, demonstration of a binding site for a receptor on DNA does not necessarily mean that the binding plays a role in the regulation of transcription. The critical role for the MMTV GRE was established by making an artificial gene containing the MMTV 5' sequence fused to a dihydrofolate reductase reporter gene; when this artificial gene was inserted into mouse L cells containing the glucocorticoid receptor the enzyme became glucocorticoid inducible (20). The capacity for glucocorticoid induction is independent of orientation of the steroid regulatory element and almost independent of the distance between the response element and the promoter at least up to 7 kilobases. The GRE can either be upstream or downstream of the polyadenylation signal. Mutations in the consensus sequence of the GRE obliterate the GRE function.

It is of interest that the site of integration of the MMTV DNA into the chromosome affects the transcription potential, the replication of some viruses being glucocorticoid inducible and others not (21). Whether a specific viral DNA insert is inducible may relate to whether sites within the GRE region are methylated (22), or it may have to do with whether nucleosomes are free to bind the GRE element (23). Another factor that is critical to hormone action is the amount of intracellular glucocorticoid receptor; glucocorticoids cause a greater transcriptional response in cell lines constructed to express supraphysiological amounts of glucocorticoid receptor (24).

The great unresolved issue is exactly how these steroid response elements work to enhance transcription. The Chambon group has proposed that the promoters for most steroid hormone-responsive genes are under negative control and that this negative control is relieved by binding of the hormone-receptor complex (25), but even at the simplistic level this explanation is not very helpful because in some instances steroid hormone inhibit rather than stimulate gene transcription (26). Some current theories about how the receptors, the steroid regulatory elements, and other transcription factors interact have been reviewed by Beato (27).

Glucocorticoid Resistance

Complete resistance to the action of glucocorticoids would almost certainly be lethal, but partial resistance was described in 1976 by Vingerhoeds, Thijssen, and Schwarz in a 55 year old man who had markedly elevated levels of plasma cortisol (face and total) and elevated levels of plasma adrenocorticotropin (ACTH) (28). The man was hypertensive and hypokalemic but had no symptoms or signs of Cushings syndrome over a 3 year period of observation. The possibility of the formation of an abnormal steroid was excluded, and it was shown that the elevated cortisol secretion was pituitary dependent and that aldosterone secretion was appropriately suppressed in response to salt loading. The authors concluded that the fact that the patient secreted 110-140 mg of cortisol per day for long periods without any evidence of Cushings disease indicated diminished sensitivity of the peripheral tissues to glucocorticoid but not to mineralocorticoids. Support in favor of this thesis was obtained by documenting that treatment with sufficient dexamethasone to suppress ACTH and to diminish cortisol production caused the hypokalemia and hypertension to disappear (28). In a subsequent study it was demonstrated that

the hypertension and hypokalemic alkalosis were in large part due to overproduction of deoxycorticosterone by the adrenal as a consequence of the elevated ACTH levels (29). The family of the index case was also studied (28-31), and it was shown that the disorder is associated with variable expressivity but is transmitted as a single gene trait, presumably codominant. The fact that affected individuals are heterozygotes and carry one normal allele probably makes the disorder compatible with life.

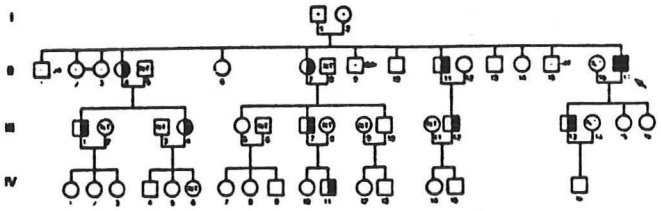


Figure 6. The pedigree of the original family with cortisol resistance. The propositus is shown by the arrow (31).

Cortisol resistance has subsequently been reported in four additional families (32-37). Hypertension was present in one of the families (37), and the index in another family was a 46 year old woman with virilizing signs thought to be secondary to overproduction of adrenal androgens (36). However, for the most part the diagnosis is made by accident.

In four of the five families the glucocorticoid receptors have been studied in lymphocytes and/or cultured skin fibroblasts. In a Japanese family, the receptor was diminished to half normal levels but appeared to be normal kinetically (32-34). In the remaining three families the amount of receptor appears to be normal, but it contains a qualitatively abnormal component. In the original family the receptor has a diminished binding affinity for ligand (29, 30), in one family the receptor is thermolabile (36), and in one family the hormone-receptor complex transforms inefficiently to the DNA-binding state (37). These findings are in keeping with the heterozygous transmission of one normal allele and a mutant allele that specifies a receptor with impaired hormone binding or some other qualitative defect.

In none of these families has the molecular defect been defined. However, molecular defects have been elucidated in several mouse lymphosarcoma lines that are resistant to killing by glucocorticoids because of mutations of the glucocorticoid receptor (38-40). On the basis of functional studies these mutations have been classified into several subtypes - failure to bind glucocorticoids, reduced interaction with DNA, increased interaction with DNA, and a putative post-receptor defect. It is now clear that the first three types of these mutations are the result of mutations in the hormone-binding domain, the DNA-binding domain, and the functional domain respectively (8, 40). The nature of the post-receptor defect (the so-called deathless mutant) has yet to be elucidated. On the basis of these studies and the limited functional studies of the defects in human glucocorticoid resistance it seems safe to predict that

the human disorder is genetically heterogeneous and that amino acid substitutions in the various domains of the gene are responsible for the disorder.

Mineralocorticoid Action

As stated above, two types of receptors for adrenal steroids were delineated on the basis of the binding of radiolabeled hormones. Mineralocorticoid receptors in crude kidney homogenates bind aldosterone and corticosterone with fairly high affinity and bind dexamethasone with much lower affinity. In contrast, liver homogenates bind dexamethasone and triamcinolone with higher affinity than corticosterone or aldosterone (41). This issue became blurred when Bruce McEwen and his colleagues described a second glucocorticoid receptor in rat hippocampus homogenates that binds corticosterone preferentially over dexamethasone (42), and it was subsequently established that the brain glucocorticoid receptor and the renal mineralocorticoid receptors are the same (42, 43). The confusion about this issue was not clarified until the role of 11-beta-hydroxysteroid dehydrogenase in glucocorticoid action was established. It is now clear that glucocorticoid can act via mineralocorticoid receptors in tissues such as brain that do not contain 11-beta-hydroxysteroid dehydrogenase whereas in tissues that actively oxidize the 11-hydroxyl group only mineralocorticoids can interact with the mineralocorticoid receptor. Stated in another way, at physiological concentrations aldosterone acts only via the mineralocorticoid receptor whereas some actions of glucocorticoids are mediated via the glucocorticoid receptor and others via the mineralocorticoid receptor.

The molecular cloning of the cDNA for the mineralocorticoid receptor revealed that it is also a typical member of the steroid-thyroid receptor superfamily (44). The gene for the receptor is located on chromosome 4, and the structure possesses a high degree of homology with the glucocorticoid receptor, namely 94% homology in the DNA-binding domain and 57% homology in the steroid-binding domain but only 15% homology in the immunological domain (44). As was predicted on physiological grounds the receptor binds progesterone at one order of magnitude lower than aldosterone, thus explaining the antagonist action of progesterone on aldosterone action.

Pseudohypoaldosteronism

A form of congenital renal salt loss associated with insensitivity to mineralocorticoids was described by Cheek and Perry in 1958 (45), and many patients with this syndrome which has come to be known as pseudohypo-aldosteronism have been described subsequently (4, 45B). Indeed, on the basis of the number of case reports this disorder appears to be relatively common. The characteristic patient is an infant who fails to thrive, is found to be hyponatremic and hyperkalemic, and loses sodium in the urine. There is a dramatic clinical improvement when adequate amounts of saline are administered. Adrenal function and ordinary parameters of renal function are normal. Indeed, aldosterone secretion is high. In infants renal salt loss does not improve after the administration of mineralocorticoids. In some patients sweat gland function is normal (45) whereas in others salivary gland, colon, and sweat glands appear to be involved (46, 47).

A special and consistent feature of the disorder is the fact that the clinical manifestations - particularly the renal salt loss - ameliorate with

time. However, one patient who was studied at age 9 after the recovery from salt loss still exhibited elevated aldosterone secretion and high plasma renin (48). Similar findings were reported in a long-term followup of the original patient described by Cheek and Perry (49). Thus, the fundamental defect of hyporesponsiveness to aldosterone is compensated in the steady state almost completely by a massive increase in endogenous production of aldosterone. In part, however, the improvement with age may be due to changes in renal responsiveness to aldosterone despite persistence of the underlying abnormality.

Many of the early cases were sporadic in nature. However, families have now been described in which the disorder appears to be inherited in an autosomal dominant fashion (51-52). The sporadic cases are probably a mixture of autosomal recessive mutations and new dominant mutations (53, 54).

The pathogenesis of this disorder is less well understood than is glucocorticoid resistance. The data are compatible with a partial defect in the aldosterone receptor (qualitative or quantitative) that can be compensated by increased levels of hormone. The first attempts to characterize the mineralocorticoid receptor in colon biopsies from patients with the disorder revealed no abnormality (48) or minor changes in affinity of binding ligand (53). However, Armanini et al (55) measured the mineralocorticoid receptors in mononuclear leucocytes from three patients with the disorder and found a deficiency in all three; in two unrelated patients the receptor appeared to be completely absent, and in the other the level was profoundly decreased (55).

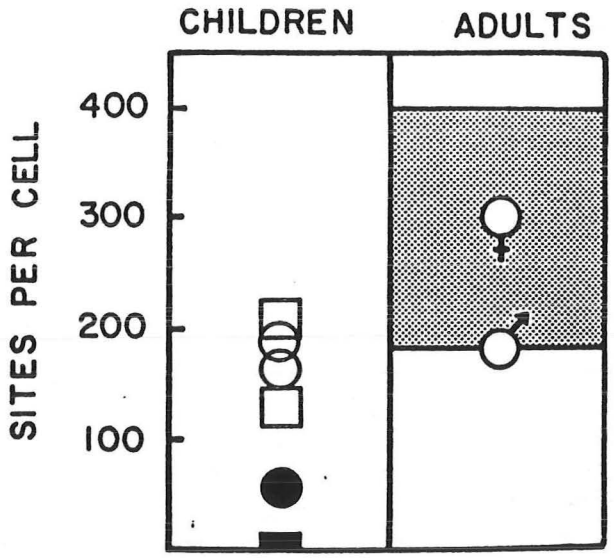


Figure 7. Concentration of mineralocorticoid receptor in mononuclear leucocytes from two siblings with pseudohypoaldosteronism (closed figures) (55B).

The molecular bases of the receptor defects have not been defined.

ANDROGEN

Dihydrotestosterone and Testosterone Action

The fact that androgens work via intracellular receptors that localize in the nucleus was among the first such demonstrations for any hormone (56). As in the case of the hormones of the adrenal cortex the action of androgens is complicated by the metabolism of the hormone. Testosterone, the major androgen secreted by the testis and the primary circulating androgen in men, serves as a circulating precursor for dihydrotestosterone, which in turn mediates many of the physiological processes involved in androgen action. (Testosterone can also be converted in extraglandular tissues to estrogen which in turn acts via the estrogen receptor.) A second distinctive feature of androgen action is that androgen plays a critical role in male sexual differentiation during embryogenesis. On the basis of a variety of types of studies, including time sequence studies in normal embryos, studies in patients with deficiency of the 5-alpha-reductase enzyme that converts testosterone to dihydrotestosterone, and studies of the effects of inhibitors of the 5-alpha-reductase enzyme, it was established that some androgen actions are mediated by testosterone and some by dihydrotestosterone. For example, certain actions in embryos (virilization of the wolffian ducts) and in postnatal life (regulation of the secretion of luteinizing hormone by the pituitary and the initiation of spermatogenesis) are mediated by testosterone itself whereas other functions of the hormone require dihydrotestosterone formation (formation of the external genitalia and male urethra during embryogenesis and virilization at the time of puberty). Whereas dihydrotestosterone can substitute for testosterone - for example, in virilizing the wolffian ducts of embryos - the opposite is not true.

Initially it was assumed that the different actions of the two hormones might be mediated by different receptors (57). However, Tfm mice, which, as the result of a single X-linked gene mutation have a functional absence of the androgen receptor, are equally resistant to testosterone and to dihydrotestosterone (58). Thus, it seems clear that one receptor must mediate the actions of both hormones. Exactly how different actions could be mediated by different hormones working via the same receptor has been a perplexing problem. Dihydrotestosterone binds to the receptor more tightly than testosterone, as manifested by a much slower dissociation rate; as a consequence under circumstances approximately the steady state dihydrotestosterone binds preferentially to the receptor. However, when the tissue level of testosterone is raised to supraphysiological levels (from 2 nM to 20 nM) testosterone appears capable of mediating androgen actions that at physiological levels of hormone require dihydrotestosterone formation (59). At present we believe that testosterone at high concentration is capable of overcoming its weaker capacity to bind to the receptor by mass action. Why some actions of the hormone require amplification of the signal whereas others do not will not be clear until the various regulatory elements that bind the androgen-receptor complexes are identified and studied in vitro.

The androgen receptor has never been purified, and it was the last of the major receptors of this family to be cloned. However, within the past year the cDNA for the receptor has been cloned in four laboratories, including our own (60-66). The structure of the receptor as predicted from the nucleotide sequence is somewhat surprising in that it contains three long arms of repeating amino acids - one of glutamine, one of glycine, and one of proline.

Disorders of Androgen Receptor Function

The gene for the androgen receptor is located on the long arm of the chromosome, now known to be between Xq11- and Xq12 (67, 68). The X-linkage of the gene - and of mutations that impair androgen receptor function has made it relatively easy to identify and study disorders of the androgen receptor, since affected XY individuals express only the mutant protein. Furthermore, because androgen action is essential for development of the male phenotype during embryogenesis and for spermatogenesis, disorders of the androgen receptor usually cause anatomical and/or reproductive problems in affected males and hence are very likely to be ascertained by physicians. For these various reasons we know more about disorders of the androgen receptor than about any of the other disorders under discussion. This subject has been discussed previously at these rounds (November 8, 1973; August 9, 1979; June 17, 1982) and in several recent reviews (56, 69, 70). In brief, disorders of androgen receptor can result in a spectrum of phenotypic abnormalities depending on the severity of the functional impairment: testicular feminization, the Reifenstein syndrome, the infertile man, and the undervirilized man. Despite differences in clinical manifestations, these disorders are similar in regard to endocrinology, X-linked inheritance, and pathophysiology.

The complete form of testicular feminization has been recognized as a distinct entity for many years. Patients are phenotypic women who come to medical attention because of inguinal hernias (infants) or because of primary amenorrhea (adolescents). The phenotype is that of a normal woman except that axillary and pubic hair are diminished. Breast development and distribution of body fat are feminine; the external genitalia are unambiguously female; and the clitoris is normal. The vagina is short and blind-ending; the uterus and fallopian tubes are absent; testes are located in the abdomen, the inguinal canal or labia majora. Spermatogenesis is absent.

About a tenth of patients with the syndrome have so-called incomplete testicular feminization in which genital hair is normal, slight clitoromegaly may be present, and there is a deep posterior forchette due to some posterior fusion of the labioscrotal folds. The vagina is short and blind-ending, but in contrast to the complete form of the disorder male wolffian duct structures can be identified.

The term Reifenstein syndrome is applied to a variety of disorders of male development in which the defective virilization within an individual family can range from men with gynecomastia and azoospermia to men with hypospadias to men with a pseudovagina. The common phenotype is that of a man with perineoscrotal hypospadias, azoospermia, and gynecomastia. The male ejaculatory ducts are hypoplastic.

The other two disorders of receptor function - the infertile male and the recently characterized underandrogenized male (71) result from even more subtle disorders of receptor function.

An abnormality of the androgen receptor in skin fibroblasts cultured from patients with testicular feminization was first reported by Keenan and coworkers (72) and has been confirmed in several laboratories. It has subsequently been established that defects of the androgen receptor can be demonstrated in genital

skin fibroblasts cultured from patients with each of these various disorders (70), and to the extent that such studies have been undertaken all mutations that cause defects of the androgen receptor are X-linked (67, 68, 73) and appear to be located in the same region of the X chromosome (67, 68). Thus, it is widely assumed that these disorders are allelic mutations of the structural gene that encodes the normal androgen receptor (70).

The original patient with complete testicular feminization whose androgen receptor was assessed had virtually complete absence of binding (72), thus explaining the profound resistance to androgen action in this disorder. However, as more and more subjects with androgen resistance have been studied it is now apparent that qualitative and/or partial quantitative defects are more common then complete absence of receptor binding (70). Some of the functional assays that have been used to identify qualitative defects are shown in Table 1.

Table 1. Functional manifestations of qualitative abnormalities in androgen receptors (Ref. 70).

Marker
1. Thermolability in monolayers
2. Instability of cytosol receptor
3. Decreased affinity of ligand binding
4. Impaired nuclear retention of ligand
5. Failure of up-regulation of the androgen receptor by androgens
6. Increased rate of dissociation of ligand from receptor
7. Lability of the androgen receptor under transforming conditions

These functional parameters include thermolability of binding in intact fibroblasts, instability of the receptor in the presence of molybdate, decreased affinity of ligand binding to the receptor, impaired nuclear retention of the hormone-receptor complex, failure of androgens to up-regulate the amount of androgen receptor, increased rate of dissociation of ligand from receptor, and lability of the androgen receptor under conditions that normally transform the hormone-receptor complex to the DNA-binding state.

The characteristics of the androgen receptor in fibroblasts from patients from 102 families who fulfill the phenotypic and endocrine requirements of androgen resistance and who have been studied in our laboratory are shown in Figure 8.

RECEPTOR DEFECTS IN FIBROBLASTS FROM 102 FAMILIES WITH ANDROGEN RESISTANCE

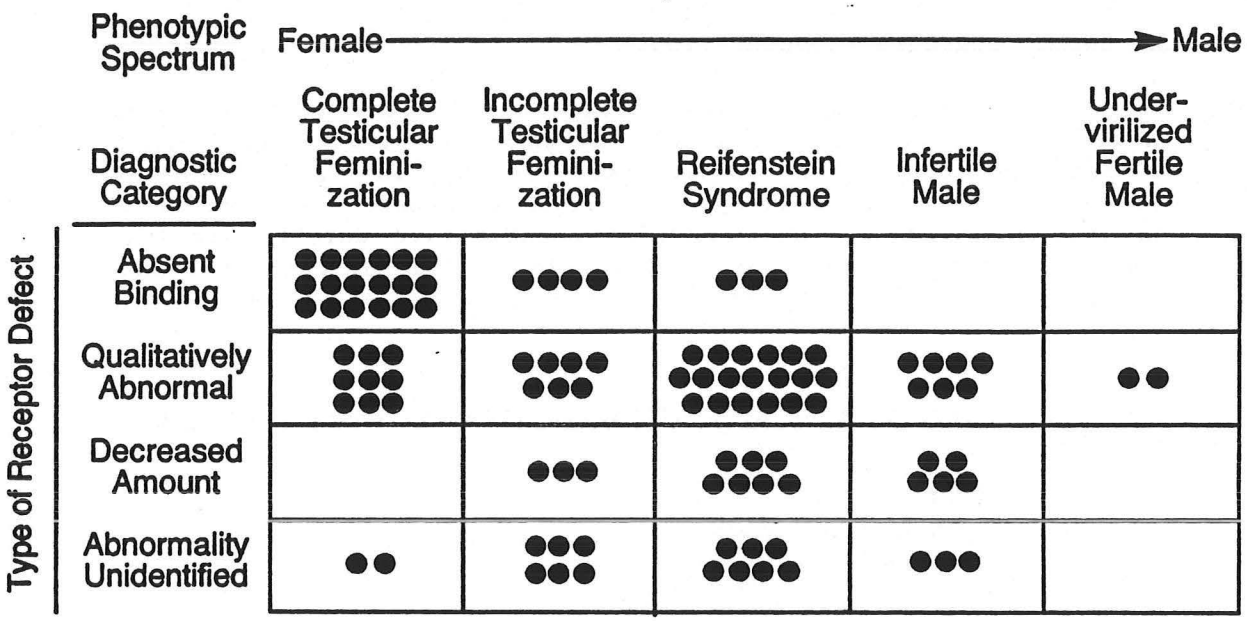


Figure 8

This includes 29 individuals or families with complete testicular feminization, 20 with incomplete testicular feminization, 36 with Reifenstein syndrome, and 17 with isolated infertility or undervirilization. Receptor has been designated as qualitatively abnormal by one or more of the criteria listed in Table 1 and as decreased amount when the amount of binding is lower than normal but when no qualitative defect can be identified. Subjects with each of these categories of defect as measured in vitro span a wide range of phenotypic abnormalities - for example, qualitatively abnormal receptors can cause complete testicular feminization on the one hand and trivial undervirilization of men on the other. Intuitively, the functional defects in the subjects with complete testicular feminization must be more severe than those in phenotypic men. The defect in the group labeled abnormality unidentified has not been identified despite endocrine and/or phenotypic evidence of androgen resistance; these patients either have as yet unrecognized qualitative defects in receptor function or defects at some distal step in androgen action.

In order to make more specific correlations between the various phenotypic defects and the nature of the abnormality in the androgen receptor, it will be necessary to identify the specific defects in the receptor molecule. Several laboratories including our own are involved in such studies, but only one such study has been reported (74). In one family with the complete form of testicular feminization who fell within the absent binding category, there was a

partial deletion of the steroid binding domain of the gene so that any mRNA transcribed and any transcribed protein product would be shorter than normal (74). The majority of such defects - even those in the absent binding category - do not appear to involve major deletions and/or gene rearrangements and are believed to be due to single amino acid substitutions in the receptor molecule.

VITAMIN D

Vitamin D Action

The major biological actions of vitamin D in mediating calcium homeostasis are mediated by a series of hydroxylated metabolites (75, 76). These metabolites are either formed from vitamin D_2 that is ingested in food or from vitamin D_3 that is formed in skin by the action of ultraviolet light on 7-dehydrocholesterol. In either case the hydroxylated forms of vitamins D_2 and D_3 are found within the body and are classified as hormones. The most important of the vitamin D metabolites is thought to be $1,25\text{-}(OH)_2$ vitamin D, which regulates calcium absorption in the kidney and, together with parathyroid hormone, causes calcium reabsorption in the kidney and stimulates the mobilization of calcium from bone (76, 77). The actions of $1,25\text{-}(OH)_2D$ are mediated through an intracellular receptor that was characterized as a high affinity, low abundance protein with the use of radiolabeled $1,25\text{-}(OH)_2D$ as the binding ligand. cDNAs for the chicken (77), rat (78), and human (79) - $1,25\text{-}(OH)_2D$ receptors have now been cloned, and the receptor bears close homology to the thyroid hormone receptor. The regulatory elements for the control of gene expression by the hormone-receptor complex have not been identified (79).

Vitamin D Resistance

The disorders of vitamin D metabolism have been classified with a confusing nomenclature. In brief, four general types of rickets and/or osteomalacia are recognized - vitamin D deficiency (whether due to diminished intake, intestinal malabsorption, or other predisposing cause), vitamin D resistant rickets (actually not a disease of vitamin D action but an X-linked disorder of phosphate metabolism), and two types of so-called vitamin D-dependent rickets. Type I vitamin D-dependent rickets is an autosomal recessive defect that impairs the 1-alpha-hydroxylase reaction by which 25-OH-D is converted to $1,25\text{-}(OH)_2D$ in kidney; this disorder can be cured by the administration of physiological amounts of $1,25(OH)_2D$ (1 μg/dy) or by giving massive doses of 25-OH-D or vitamin D itself.

Vitamin D-dependent rickets type II is also a rare autosomal recessive disease in which hypocalcemia, secondary hyperparathyroidism, and rickets become manifest in childhood, frequently in the first year of life. The disorder may be present in siblings, and about 40% of patients are the offspring of consanguineous marriages. In half or more alopecia totalis is present. Plasma levels of $1,25\text{-}(OH)_2D$ are high (80), but most patients do respond to supraphysiological doses of vitamin D or of $1,25(OH)_2D$ (81).

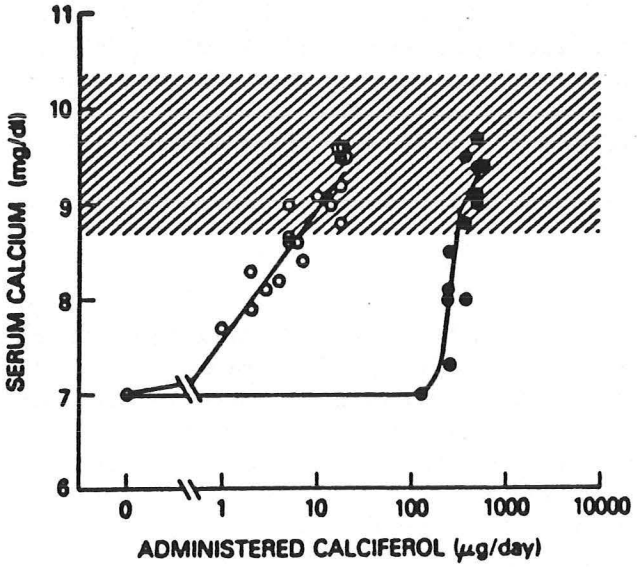


Figure 9. Steady state serum calcium in a patient with vitamin D-dependent rickets type II as a function of maintenance dose of vitamin D_2 (●) or $1,25\text{-}(OH)_2D_3$ (O) (82).

Hence, the eponym vitamin D responsive rickets.

It was widely assumed that the pathogenesis of this disorder resides at the level of the receptor for $1,25\text{-}(OH)_2D$ or at some post-receptor level, and indeed the receptor appears to be absent or profoundly deficient in fibroblasts from some patients (83-85). However, the disorder is genetically heterogeneous, analogous to that situation in androgen resistance. In other families the receptor appears to be qualitatively abnormal; namely, although it binds the hormone-receptor complex normally, the hormone-receptor complex does not bind to DNA with normal affinity (83, 84, 86-88). Likewise, Griffin and Zerwekh described a patient whose receptor appeared to be qualitatively normal despite clear-cut resistance to hormone action in vivo and in vitro, raising the possibility of post-receptor resistance (89). In additional families the defect has not been defined (84, 90).

The molecular defect has been defined in two unrelated families in whom the defect is diminished affinity of binding of the hormone-receptor complex to DNA. Genomic DNA from these patients was amplified, and each of the nine exons encoding the receptor protein was sequenced; in each family, a different single nucleotide mutation was found in the DNA-binding domain of the protein (91):

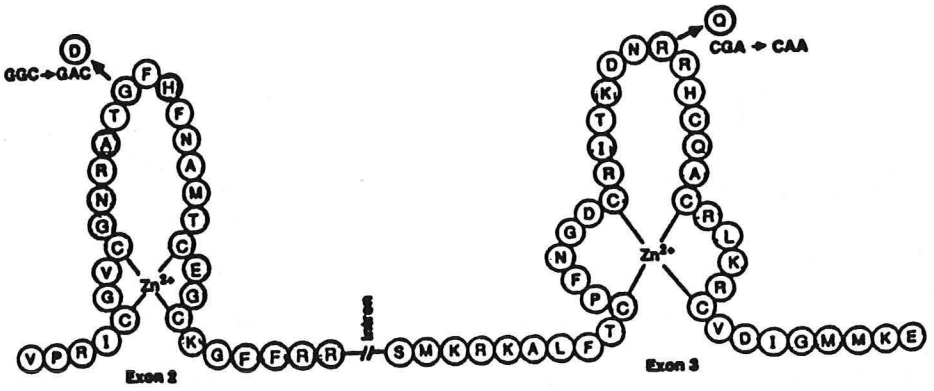


Figure 10. The deduced amino acids from the normal DNA binding domain of the vitamin D receptor and the mutations defined for two families with vitamin D resistance (91).

When the mutant cDNAs were transfected into COS-1 cells, the expressed protein was indistinguishable from the mutant receptor isolated from patients. This represents the most advanced analysis of any of the receptor mutations now available.

THYROID HORMONE

Thyroid Hormone Action

The action of thyroid hormone is similar to that of steroid hormones. Triiodothyronine, the active metabolite, can be formed from thyroxine either in the pituitary or in extraglandular tissues. While there is some evidence for cell surface, mitochondrial, and cytoplasmic binding of thyroid hormones (92), the free hormone is believed to gain access to the nuclei of target tissues where the unoccupied receptor is located (93, 94). The triiodothyronine receptor is widely distributed in tissues (with a few notable exceptions such as spleen and testis), and the number of receptors per nucleus is between 2000 and 6000. The receptors have a particularly high affinity (kD around 10^{-10}M). Thyroxine binds to the receptor about a tenth as well as triiodothyronine.

The receptor was never purified by chemical means, but with the use of photoaffinity labeling techniques it was established that many cells contain two forms of receptor - of 47,000 and 57,000 MW - that appear to bind ligand with similar affinities. The functional significance of these two forms is not clear, e.g., whether they represent different forms of the same precursor, are the product of alternate splices of the same gene, or are produced by separate genes.

The issue became even more complicated when the cDNA for the receptor was cloned. The erb A oncogene on chromosome 3 encodes a thyroid hormone receptor in human placenta (95), and a similar product is present in chick embryo (96). This cDNA is translated into 55,000 and 52,000 M proteins as predicted by

different start codons in the open reading frame, and the relative binding affinities for thyroid hormone analogues are similar to those predicted from physiological action.

Subsequently, additional cDNAs for thyroid hormone receptors have been cloned. The first was another c-erb-A related cDNA from a rat brain library (97). This cDNA hybridizes to human chromosome 17; the mRNA product of the gene is expressed in many tissues but not in liver, and the translated protein receptor binds hormone analogues with no physiologic function (triiodothyroacetic acid) with the same affinity as triiodothyronine. To further complicate this issue an erb A derived cDNA has been cloned from a human testis library that encodes a protein with high homology to the one from chicken (98). Furthermore, Nakai and his colleagues have cloned a fourth thyroid hormone receptor that is related to the erb A class and that is expressed in human liver, kidney, liver, placenta and brain (99). This receptor binds triiodothyronine with a Kd of 10^{-9} M, and the gene maps to chromosome 17. The latter authors divide these various thyroid hormone receptors into two classes:

1.) Alpha type refers to the receptors described in chicken embryo (96), rat brain (97), and human kidney (99). These receptors are highly homologous, and the cDNAs from all three hybridize to human chromosome 17.

2.) Beta type refers to the receptor described in human placenta and is encoded on human chromosome 3.

Whether additional genes exist for thyroid hormone receptors is not known (5, 94, 99). To further complicate matters, tissue specific processing of the primary transcripts of these genes vary so that different species of mRNAs and of receptor can be formed in different tissues from the primary transcripts of each of these genes (99).

The mechanisms by which the triiodothyronine-receptor complexes alter gene expression have been reviewed by Samuels (94). In brief, more is known about this system than for any other except glucocorticoids. As is true for steroid hormones, transcription of some responsive genes is stimulated, and transcription of others is inhibited by the hormone. The expression of each response gene is tissue specific and must involve tissue specific trans- and cis-acting elements. The experimental system that has been studied in greatest detail is the regulation of the growth hormone gene in cultured rat pituitary cells. At least four thyroid regulatory elements have been identified in the 5' flanking sequence of the gene.

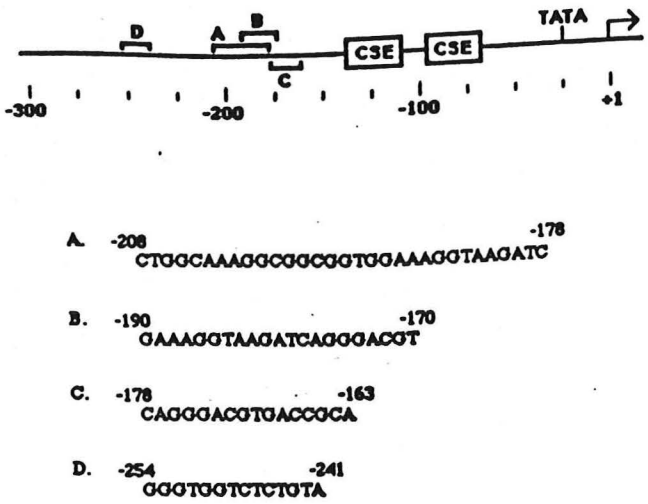


Figure 11. Candidate thyroid regulatory element sequences in the 5' flanking region of the rat growth hormone gene (94).

It is Samuels's interpretation that the A region functions as the thyroid hormone response element, but the exact mechanism by which this occurs and the identity of the other factors involved have not been identified.

Thyroid Hormone Resistance

In view of the complexity of thyroid hormone action and in particular of the thyroid receptor system it is to be expected that thyroid hormone resistance would be complex and genetically heterogeneous (100-102). The most convenient classification is to divide the disorder into global or generalized resistance and selective or limited resistance. Alternatively, it can be classified as severe, mild, or selective:

Table 2. Classification of thyroid hormone resistance syndromes (Ref. 4).

Disorder	Inheritance	Neurosensory Deafness	Stippled Epiphyses	Delayed Bone Age	Goiter	Endocrine Profile			Nuclear T_3 Binding
						Plasma T_4	Plasma T_3	Plasma TSH	
Severe resistance	Autosomal recessive	+	+	+	+	↑	↑	N*	High affinity binding one-tenth normal
Mild resistance	Autosomal dominant	–	–	±	±	↑	↑	N*	Normal
Selective resistance of pituitary	Unknown	–	–	–	+	↑	↑	↑	Unknown

*High in relation to circulating T_4 and T_3 levels.

Global resistance was first described by Refetoff and his colleagues (103-106) as an autosomal recessive trait in 3 siblings from a consanguineous marriage.

The children had goiters associated with high levels of plasma thyroid hormones, elevated plasma TSH; in addition, they had congenital deafmutism, stippling of the epiphysis, and nystagmus. A similar unrelated sporadic case was reported in 1980 (106A), but most of the subsequently reported 60+ patients are not so severely affected as the autosomal recessive variety (100-102). The usual patient with global resistance is a child with congenital goiter, elevated TSH and thyroid hormone levels, and slightly retarded bone age. At the metabolic level patients may be euthyroid or mildly hypothyroid. About half of the mild cases are familiar, and half are sporadic, and when the family history is positive the disorder appears to be transmitted as a single unit tract (dominant or codominant). Because of the presence of a goiter (secondary to increased TSH levels) and high plasma thyroid hormone values, some patients have been misdiagnosed as hyperthyroid and subjected to ablative therapy. In most studies patients can be made clinically euthyroid if given supraphysiological amounts of triiodothyronine. Typical laboratory data from a family with the mild autosomal dominant disorder are illustrated in Table 3.

Table 3. Thyroid function tests in one kindred with autosomal dominant thyroid hormone resistance (107).

Patient	Age (yr)	Serum T4 (μg/dl)	Serum FT4 (ng/dl)	Serum T3 (ng/dl)	Serum FT3 (pg/dl)	Serum rT3 (ng/dl)	Serum TSH (μU/ml)	Serum TBG (mg/dl)	Serum Cholesterol (mg/dl)	TBG Binding Capacity (μg T4/dl)	Resin T3 Uptake (%)	Thyroid ^{131}I Uptake (%)
JR	3.5	21.8	6.9	329	1,701	84	2.3	5.0	198	24	36	38
CR	27	19.9	5.1	279	1,385	75	6.3	4.2	192	22	37	45
HC	64	17.6	5.2	261	799	78	13.3	5.0	171	20	34	28
AS	40	21.1	5.2	290	727	88	1.7	4.0	207	19	31	26
WC	33	20.5	6.5	258	828	88	0.5	4.5	178	16	40	41
SC	8	20.7	4.6	357	1,085	90	1.0	4.5	148	17	40	45
BC	5	25.1	5.2	404	1,061	115	4.5	5.8	170	25	34	34
PC*	20	21.9	4.5	406	1,485	85	1.0	6.3	205	33	30	26
Normal adult		5–12	1.3–3.8	80–160	220–660	30–80	0.5–4.0	2.1–5.2	180–250	10–26	25–35	10–30

NOTE: T4 = thyroxine; FT4 = free T4; T3 = triiodothyronine; FT3 = free T3; rT3 = reverse T3; TSH = thyrotropin; TBG = thyroxine-binding globulin; ^{131}I = radioactive iodine.
* Patient taking oral contraceptive (1 mg ethynodiol diacetate and 50 μg ethinyl estradiol).

Selective pituitary resistance to thyroid hormones is associated with signs and symptoms of hypothyroidism because the elevated TSH level leads to elevated secretion of thyroid hormones and a mild thyrotoxicosis (100-102). Since the resistance to thyroid hormone action appears to be limited to the pituitary the clinical features of hyperthyroidism may be sufficiently severe in some as to warrant ablative therapy. At the clinical level, the disorder is difficult to separate from TSH-secreting pituitary adenomas, and it may be that the diagnosis is frequently overlooked.

In view of the fact that selective resistance is not manifested in extraglandular tissues and in view of the fact that those individuals with the autosomal dominant, mild form of the generalized thyroid hormone resistance have one normal allele and hence on average half levels of normal receptor, it is not surprising that convincing evidence for an abnormality of the thyroid hormone receptor has been obtained only in a few patients; indeed, some patients with

the mild autosomal dominant disorder may actually have defects in thyroid hormone transport or metabolism (109) whereas others appear to have half normal levels of normal receptor (110).

However, clear-cut kinetic abnormalities of receptor function have been reported in two families - the original family reported by Refetoff (105) and in two siblings from another family (111).

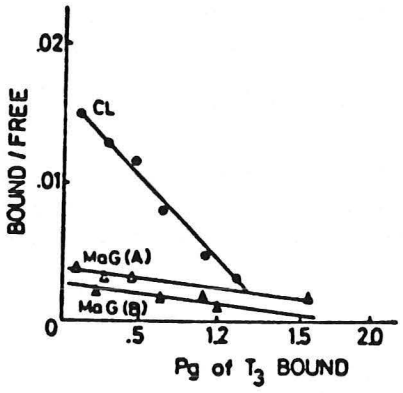


Figure 12. Scatchard plots of the binding of triiodothyronine to nuclear receptors in lymphocytes from a patient with the autosomal recessive form of thyroid hormone resistance (105).

The DNA for this family is now being sequenced with the assumption that it involves the alpha receptor (99).

PROGESTERONE

The cDNA for the progesterone receptor has been cloned from chicken (112-114), rabbit (115) and human (116). The human receptor maps to the long arm of chromosome 11 (117). The gene is transcribed into more than one species of mRNA. The chromosomal structure of the chicken progesterone receptor gene consists of eight exons and is approximately 38 kilobases long (118). Transcription start sites are 360 base pairs upstream from the first translate initiation codon of the first exon. Most interestingly, the putative promoter region lacks a typical TATA box homology but does contain CLGCCC motifs, compatible with the fact that the transcription of the gene is under the control of estrogen (112).

Resistance to the action of progesterone was described by Keller et al in a 23 year old woman who was evaluated for infertility and who appeared to have a syndrome of inadequate corpus luteum function (119). Failure of the endometrial stroma to undergo pseudodecidual reaction was documented in repeated endometrial biopsies during the late luteal phase of the cycle. However, despite the persistent abnormal endometrial biopsy, the endocrine pattern of the cycles was normal with normal plasma levels of progesterone, estradiol, LH, and FSH. Exogenous progesterone did not correct the abnormality, and there was a family history of female infertility in preceding generations. The amount of high affinity progesterone binding in endometrial cytosol extracts

was half that of preparations from normal control subjects (119). Thus, the incomplete maturation of the endometrial stroma is believed to have resulted from resistance to progesterone action within the uterus. The molecular basis for this presumed defect is unknown.

ESTROGEN

The cDNA for the human estrogen receptor was among the first to be cloned (120-122), and cDNAs for the homologous receptors in chicken (123-124) and in xenopus (125) were subsequently cloned. The functional domains of the human estrogen receptor are similar to those of the other members of this family (126). The estrogen-receptor regulatory element for the vitellogenin gene has been identified and consists of a consensus sequence 38 nucleotides long that contains an inverted repeat 5'CAGGTCAGAGTGACCTG3'.

It is striking that resistance to estrogen action has never been described. Estrogen action is believed to be essential for implantation of the blastocyst (128), and if so, any mutation that severely impaired the action of estrogen would almost certainly be lethal.

CONCLUSIONS

A common feature of hormone resistance syndromes is the presence of a normal or elevated level of the hormone in the circulation. This feature is the consequence of the fact that hormones are under regulatory feedback control, and failure of hormone action usually leads to increased hormone production. Since partial defects in hormone action may be compensated by increased hormone levels, little, if any, clinical symptoms may be produced. Nevertheless, hormone resistance should be suspected whenever hormone levels are inappropriately high for the clinical state. It follows that a large number of defects must go unrecognized and that the more subtle the change in receptor number or receptor function the more difficult it will be to diagnose the state.

As summarized in Table 4, genetic heterogeneity of several types occurs in these disorders. Both dominant and recessive forms exist for several of the receptor defects, and it may well be that many or most mutations of the androgen receptor are "private" mutations that differ in each affected family. Another type of heterogeneity exists at the target tissue level since patients with some receptor abnormalities (thyroid and androgen) appear to be more resistant in some tissue than in others. These differences in target tissue expression doubtlessly explain how hormone resistance in some tissues can coexist in some disorders with symptoms of hormone excess in others.

Table 4

Characteristics of Disorders of Intracellular Receptor Function

Receptor (Chromosome)	Disorder	Clinical Manifestations	Genetics	Laboratory Features
Glucocorticoid (5)	Cortisol Resistance	Few	Autosomal Dominant or Codominant	Elevated Plasma Cortisol and Increased Cortisol and ACTH Secretion
Mineralocorticoid (4)	Pseudohypoaldosteronism	Salt Wasting in Infancy	Variable, Autosomal Recessive; Autosomal Dominant	Elevated Plasma Aldosterone, Renin, and Angiotensin
Androgen (X)	Testicular Feminization to Undervirilized Men	Variable Phenotypic Women to Undervirilized Men	X-Linked Recessive	Elevated Plasma Testosterone and Luteinizing Hormone (Usually)
Vitamin D	Vitamin D Responsive Rickets Type II	Rickets	Autosomal Recessive	Elevated $1,25(OH)_2$ Vitamin D
Thyroxine (3, 17)	Thyroid Hormone Resistance	Variable, from Hypothyroidism to Hyperthyroidism	Variable; Autosomal Recessive or Codominant	Elevated Plasma TSH and Plasma Thyroid Hormones
Progesterone (11)	Inadequate Corpus Luteum Syndrome	Failure to Undergo a Decidual Reaction	Unknown	Normal Progesterone and Gonadotropins

It is of interest that hereditary resistance syndromes for hormones that are essential for life (cortisol, thyroxine) are inevitably only partial defects; complete defects in the actions of these hormones are incompatible with life. Likewise, the more severe the defect (testicular feminization) the less likely the hormone is to be essential for the life of individuals.

Hormone resistance frequently results in developmental abnormalities (androgen, thyroid hormone, vitamin D). These developmental defects could have been anticipated from what was known about deficiency states for the various hormones, but it is noteworthy that partial defects result in less severe anatomical and developmental defects. This raises the possibility that many common birth defects (cryptorchidism, hypospadias, skeletal anomalies, deafness) may in fact result from subtle defects in hormone action during embryogenesis. Each patient with hormone resistance is a natural model for the analysis of the mechanisms by which eukaryotic genes are regulated.

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