International Union of Pharmacology. LXV. The Pharmacology and Classification of the Nuclear Receptor Superfamily: Glucocorticoid, Mineralocorticoid, Progesterone, and Androgen Receptors

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Introduction

The glucocorticoid receptor (GR[1]), mineralocorticoid receptor (MR), progesterone receptor (PR), and androgen receptor (AR) are classic members of the nuclear receptor superfamily, composing subfamily 3C. Members of this subfamily are among those receptors that were cloned the earliest, with the GR being cloned in 1985 and the MR, PR, and AR shortly thereafter (Hollenberg et al., 1985; Arriza et al., 1987; Misrahi et al., 1987; Chang et al., 1988; Lubahn et al., 1988). Individually and in combination, these four receptors play pivotal roles in some of the most fundamental aspects of physiology such as the stress response, metabolism, immune function, electrolyte homeostasis, growth, development, and reproduction.

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[1] Abbreviations: GR, glucocorticoid receptor; MR, mineralocorticoid receptor; PR, progesterone receptor; AR, androgen receptor; DBD, DNA-binding domain; LBD, ligand-binding domain; GRE, glucocorticoid response element; AF, activation function; SRC-1, steroid receptor coactivator 1; ACTH, corticotropin; CBG, corticosteroid-binding globulin; CNS, central nervous system; SHBG, sex hormone-binding globulin; HSP, heat shock protein; NCoR, nuclear receptor corepressor.

Multiple signaling pathways have been established for all four receptors, and several common mechanisms have been revealed (Mangelsdorf et al., 1995). One main signaling pathway is via direct DNA binding and transcriptional regulation of responsive genes. Another is via protein-protein interactions, mainly with other transcription factors such as nuclear factor-κB, activator protein-1, or signal transducer and activator of transcriptions, to regulate gene expression patterns. Both pathways can up-regulate or down-regulate gene expression. Both pathways require ligand activation of the receptor and interplay with multiple protein factors such as chaperone proteins and coregulator proteins (Lonard and O'Malley, 2005).

These four steroid hormone receptors also exemplify the tremendous capacity and precision of endocrine modulatory mechanisms. Patients carrying mutated receptors frequently experience severe complications, and transgenic animals lacking individual receptors frequently cannot reproduce and/or survive (Cole et al., 1995, 2001; Lydon et al., 1995; Quigley et al., 1995; Berger et al., 1998; Tajima et al., 2000; Bray and Cotton, 2003; Sato et al., 2003; Sartorato et al., 2004; Lin et al., 2005; Matsumoto et al., 2005). Temporally controlled tissue distribution patterns during developmental stages, reproductive phases, and disease states contribute to the diverse activities of these receptors. Recently, exciting new information has emerged regarding these receptors, such as their structures, domain interactions, coregulatory part-

ners, multiple isoforms, post-translational modifications, and synthetic selective modulator ligands, which show promise for new effective therapeutic approach.

Structure

The GR, MR, PR, and AR share structural similarities, with all containing three functional domains, i.e., the N-terminal transactivation domain followed by the DNA-binding domain (DBD) and the C-terminal ligand-binding domain (LBD) (Mangelsdorf et al., 1995). A hinge region links the DBD and the LBD. Compared with the GR, the sequence identities of the N-terminal domains of the MR, PR, and AR are 38, 24, and 16%, of the DBDs are 94, 91, and 79%, and of the LBDs are 57, 54, and 51%, respectively (Hollenberg et al., 1985; Arriza et al., 1987; Misrahi et al., 1987; Chang et al., 1988). Overall sequence identities for each receptor among different species (human, rat, and mouse) are between 81 and 97%.

The crystal structure of the DBD was solved for the GR (Luisi et al., 1991). The structures of the DBDs for other receptors can be inferred on the basis of the high degree of similarity of this domain among this group of receptors. Several unique features contribute to the ability of the GR DBD to bind specifically to its target DNA recognition sequences, termed glucocorticoid-response elements (GREs). The GR DBD has a single globular domain containing two perpendicular α helices, one of which is responsible for specific DNA recognition and together with the other α helix forms the cross-shaped hydrophobic core of the DBD. At the N terminus of each helix, a zinc ion coordinated by four cysteine residues in a tetrahedral geometry holds the peptide loops. The DBD, which is monomeric and unstructured in solution, dimerizes in a head-to-head orientation when it binds to DNA with the recognition helices of each DBD in adjacent major grooves of the DNA. This accounts for the cooperative binding of two DBD domains to the GRE. The precise chemistry of the protein-protein and the protein-DNA interfaces has also been elucidated (Luisi et al., 1991). The protein is anchored to the phosphate backbone with seven contacts on either side of the major groove. The DNA-recognition helix makes three van der Waals contacts between a valine and the methyl group of a thymine. Classic GREs consist of two hexameric inverted repeat half-sites separated by a 3-base pair spacer. The sequence of the half-sites determines which receptor can be recognized specifically. In nonspecific binding, the contacts made between the receptor and DNA are rearranged and fewer in number. In addition, gene-specific GR-GRE interactions have been reported. For example, it has been reported that a GR trimer binds to the pro-opiomelanocortin promoter and exerts transcription repression (Drouin et al., 1993); composite GREs recruit additional transcription factors that deter-

mine the direction of GR-mediated transcription of the proliferin gene (Diamond et al., 1990); GR forms a heterodimer with other steroid hormone receptors such as MR (Calle et al., 2003; Funder, 1993; Trapp and Holsboer, 1996) and AR (Chen et al., 1997) on some other GREs.

The crystal structures for the LBD of the GR, MR, PR, and AR have been made available through work from several groups (Williams and Sigler, 1998; Matias et al., 2000; Bledsoe et al., 2002, 2005; Kauppi et al., 2003; Fagart et al., 2005; Li et al., 2005). Remarkable similarities as well as some unique features have been identified, providing strong evidence for several important aspects of receptor function including ligand selectivity, receptor dimerization, and coactivator recruitment. One of the common features of the LBDs of the GR, MR, PR, and AR is the structural composition and organization. Each LBD contains 11 α helices (designated helix 1, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12) and four small β strands that fold into a three-layer helical sandwich. The region between helices 1 and 3 is unstructured in the steroid receptors, in contrast to the other nuclear receptors from which the nomenclature derives. Helices 1 and 3 form one side of the sandwich, and helices 7 and 10 form the other side. The middle layer (helices 4, 5, 8, and 9) is arranged at the upper half of the LBD, delimiting a hydrophobic cavity underneath where the steroid molecule is bound. Toward the C terminus, the activation function (AF)-2 helix, helix 12 packs against helices 3, 4, and 10 as an integrated part of the domain structure. Following helix 12 is an extended β strand that forms a β sheet together with a β strand between helices 8 and 9. Thus, the ligand-binding pocket has a scaffold framed by multiple helices and the first two β strands. The cognate steroid ligand for each receptor is completely buried within the ligand-binding pocket. Three structural features ensure ligand selectivity. First, the unique hydrogen bond network between the receptor and the bound ligand establishes specific recognition between the cognate ligand and receptor. For example, the MR ligand-binding pocket contains a unique polar surface absent in the other receptors, which is critical for specific binding of aldosterone. Second, the shape of the steroid and the topology inside the binding pocket enhance selectivity. The GR ligand-binding pocket contains a branched side pocket due to a proline residue in the linker between helices 6 and 7, which is critical for high-affinity binding of glucocorticoids to the GR. Third, the relative position of the binding pocket within the receptor LBD plays a role in ligand selectivity. Compared with the other receptors, the AR ligand-binding pocket seems to be shifted up toward helices 1 and 3, which contributes to selectivity of the AR for androgens. The relative position of the ligand-binding pocket provides a structural basis for the importance of residues outside of the pocket, which are critical for the integrity of the LBD (Rogerson et al., 1999).

Another common feature of the LBD among steroid receptors is the presence of the coactivator-binding cleft on the surface of the LBD above the ligand-binding pocket (Williams and Sigler, 1998; Matias et al., 2000; Bledsoe et al., 2002; Li et al., 2005). This AF-2 binding site is essential for the ligand-dependent recruitment of a wide variety of coactivators that determine transcriptional activity of the receptor. Specific charged residues termed charge clamps and intermolecular interactions facilitate relative cofactor selectivity by each receptor. A common motif among the coactivators that interacts with these charge clamp residues is the leucine-rich LxxLL motif (Lonard and O'Malley, 2005). The AR, however, prefers FxxLF motifs and interacts with lower binding affinity with the LxxLL-containing cofactors such as steroid receptor coactivator 1 (SRC-1) (He et al., 2002, 2004).

Structures of the N-terminal variable regions are not available to date for any of the receptors in this subfamily. Recent work from several laboratories suggests that this domain possibly folds into an organized structure and interacts with the C terminus of the receptor through specific intra- and intermolecular interactions (Langley et al., 1998; He et al., 1999; Tetel et al., 1999; Rogerson and Fuller, 2003). A glutamine-rich region in the AR N terminus is necessary and sufficient for recruiting coactivators such as SRC-1 (Bevan et al., 1999). Polymorphisms such as glutamine-rich tracts of abnormal length in the AR result in molecular changes and neurological disease (Poletti, 2004). Further work is needed to shed light on the molecular organization of this important domain that contributes to the transcriptional activity of the receptor.

Endogenous Ligands and Their Functions

The major glucocorticoid in the human is cortisol, also called hydrocortisone, whereas in rodents the major glucocorticoid is corticosterone. The synthesis and secretion of glucocorticoids by the adrenal cortex are tightly regulated by the hypothalamo-pituitary-adrenal axis, which is sensitive to negative feedback by circulating hormones and exogenous glucocorticoids. Healthy individuals secrete 10 to 20 mg of cortisol daily (Katzung, 2004; Goodman et al., 2006). The rate of secretion follows a circadian rhythm governed by pulses of pituitary hormone corticotropin (ACTH). In plasma, cortisol is bound to circulating proteins, such as corticosteroid-binding globulin (CBG) that binds 90% of the circulating hormone under normal circumstances. The remaining cortisol is free or loosely bound to albumin and is available to exert its effects on target cells. CBG is increased in pregnancy, by estrogen administration, and in hyperthyroidism. Synthetic glucocorticoids such as dexamethasone are largely bound to albumin rather than CBG.

GR is expressed in almost all tissues although tissue- and cell cycle-specific regulation of GR levels have been

reported (Cidlowski et al., 1990; Oakley et al., 1996; Lu and Cidlowski, 2005). Glucocorticoids exert a vast array of physiological functions via the GR. Glucocorticoids are important regulators of carbohydrate, protein, and fat metabolism (Katzung, 2004; Goodman et al., 2006). In the fasting state, glucocorticoids stimulate gluconeogenesis and glycogen synthesis via a variety of mechanisms including increasing the production of enzymes critical in gluconeogenesis, stimulating the release of amino acids from muscles, promoting insulin resistance in the peripheral tissues, and inhibiting adipokines such as adiponectin. These processes protect glucose-dependent tissues such as the brain and heart during starvation. Glucocorticoids also profoundly modulate immune responses by regulating the activity of peripheral leukocytes, by suppressing the production of cytokines and chemokines, and by changing the life span of immune cells. In addition, glucocorticoids are critical for the functions of the central nervous system (CNS), digestive, hematopoietic, renal, and reproductive systems. The development of fetal lung is dependent on glucocorticoids.

The most physiologically important mineralocorticoid is aldosterone. Aldosterone is synthesized in the adrenal cortex primarily under the regulation of the renin-angiotensin system, potassium status, and ACTH. Aldosterone is secreted at the rate of 100 to 200 μg/day in normal individuals with a moderate dietary salt intake and does not seem to be tightly bound to serum proteins (Katzung, 2004; Goodman et al., 2006). MR is expressed in epithelial tissues, such as the distal nephron or colon (Krozowski and Funder, 1983). Vectorial sodium reabsorption is driven by a mechanism coupling the apical epithelial sodium channel to sodium-potassium ATPase, the basolateral sodium pump. Both the epithelial sodium channel and Na^+,K^+-ATPase subunit genes are differentially regulated by aldosterone (Verrey et al., 1987; Kolla et al., 1999; Amasheh et al., 2000; Epple et al., 2000; Kolla and Litwack, 2000). Consequently, aldosterone promotes the reabsorption of sodium from the distal convoluted and cortical collecting renal tubules. Sodium reabsorption in the sweat glands, salivary glands, and gastrointestinal mucosa can also be increased by aldosterone. Thus, aldosterone is a critical regulator of serum sodium and other electrolytes and of cardiovascular tone. Interestingly, MR expression and function extend to nonepithelial cells such as hippocampal and hypothalamic neurons, cardiomyocytes, the vasculature, and adipocytes, with studies reporting both physiological and pathophysiological roles of MRs at these additional sites emerging (de Kloet et al., 2000; Funder, 2004). The MR is unique in that it is the receptor for two physiological ligands, aldosterone and cortisol (or corticosterone in rodents). Both have a similar affinity for MRs and, therefore, given the much higher circulating concentration, cortisol might be expected to exclusively occupy MRs. In epithelial and vascular tissues this occupation is prevented by the presence of the

enzyme 11β-hydroxysteroid dehydrogenase 2, which converts cortisol to the inactive metabolite, cortisone. Inhibition of this enzyme by mutation or ingestion of inhibitors such as licorice or carbenoxolone results in inappropriate MR activation and hypertension. In other tissues such as the heart and selected areas in the CNS, the MR may act as a receptor for cortisol.

Progesterone is the most important progestin in humans. It is synthesized in the ovary, testis, and adrenal gland from circulating cholesterol. Large amounts are also synthesized and released by the placenta during pregnancy. In the ovary, progesterone is produced primarily by the corpus luteum. In addition to having important hormonal effects, progesterone serves as a precursor in the synthesis of estrogens, androgens, and adrenocortical steroids. Normal males seem to secrete 1 to 5 mg of progesterone daily (Katzung, 2004; Goodman et al., 2006). The progesterone level is only slightly higher in the female during the follicular phase of the menstrual cycle. During the luteal phase of the cycle and in the third trimester of pregnancy, the rate of progesterone secretion increases to 10 to 20 mg/day and to several hundred milligrams during the latter part of pregnancy. In plasma, 90% or more of total progesterone is bound by albumin and CBG. PR is expressed in the female reproductive tract, mammary gland, brain, and pituitary gland (Mangal et al., 1997; Soyal et al., 2005). In many cells, estrogens induce expression of PR, and its presence is a common marker for estrogen action in both research and clinical settings. In many biological systems, progestins enhance differentiation and oppose the cell proliferation action of estrogens. The unequivocal roles of progesterone in a variety of events such as ovulation, implantation, mammary gland development, maintenance of pregnancy, and behavior are well established. Progesterone also increases the ventilatory response of the respiratory centers to carbon dioxide and decreases arterial and alveolar P_{CO_2} in the luteal phase of the menstrual cycle and during pregnancy. Progesterone has depressant and hypnotic actions in the CNS, which may be mediated via inhibitory neurotransmitter receptors. Accumulating data indicate a role for progesterone in male reproductive events (Gadkar-Sable et al., 2005).

In humans, the predominant androgen secreted by the testis is testosterone. In men, ~8 mg of testosterone is produced daily (Katzung, 2004; Goodman et al., 2006). In women, 0.25 mg of testosterone is synthesized by the ovary and by peripheral conversion of androstenedione produced by the adrenal gland. Alterations in plasma concentrations of testosterone and androstenedione occur during the menstrual cycle. In some ovarian disorders, androgens secreted by the ovary can be elevated, resulting in partial virilization. The concentration of testosterone in the plasma of males is relatively high during three periods of life: during embryonic development, during the neonatal period, and from puberty

throughout adult life. The androgen concentration starts to rise in male embryos in approximately the 8th week of development and declines before birth. Androgen rises again during the neonatal period and then falls to typical prepubertal values within the first year of life. Plasma testosterone increases again at the time of male puberty and is maintained at the adult level until it declines gradually in senescence. Approximately 40 to 65% of circulating testosterone is bound to sex hormone-binding globulin (SHBG). SHBG is increased in plasma in response to estrogen and thyroid hormone and in patients with cirrhosis of the liver. SHBG levels are decreased by androgen and growth hormone and are lower in obese individuals. Most of the remaining testosterone is bound to albumin. Approximately 2% remains free and available to enter cells and bind to intracellular AR. In AR-target tissues such as prostate and skin, testosterone is reduced at the 5α position to 5-dihydrotestosterone, which serves as the active hormone (Auchus, 2004). Unlike other steroid receptors, AR is stabilized by high-affinity binding of testosterone or 5-dihydrotestosterone that induces the N-terminal FxxLF motif binding to the AF-2 in the LBD (Langley et al., 1998; He et al., 1999). 5-Dihydrotestosterone dissociates more slowly than testosterone from AR and thereby more effectively stabilizes the AR complex.

Androgens serve critical functions at different stages of life in the male (Katzung, 2004; Goodman et al., 2006). During embryonic life, androgens virilize the urogenital tract of the male embryo, and their action is thus essential for the development of the male phenotype. Lack of a fully functioning AR due to naturally occurring mutations in the male fetus results in incomplete male genital development or a female external phenotype (Quigley et al., 1995). The role of the neonatal surge of androgen secretion is not well defined, but it may contribute to developmental functions within the CNS. At puberty, androgens stimulate the development of secondary sexual characteristics. The growth-promoting properties of androgen increase height and the development of the skeletal musculature. In addition to stimulating and maintaining sexual function in men, androgens may also be responsible in part for aggressive behaviors. Androgens have critical physiological roles in women as well. Testosterone and androstenedione are precursors for estrogen biosynthesis; testosterone and 5-dihydrotestosterone also produce androgenic effects via the AR.

Therapeutic Uses and Limitations

For several years, compounds targeting GR functions have been among the most frequently prescribed drugs. This is mainly due to immunomodulatory actions of glucocorticoids and their use in infections, allergies, eye diseases, hematological disorders, pulmonary diseases, skin diseases, inflammatory conditions of bones and joints, and acute respiratory distress syndrome (Kat-

zung, 2004; Goodman et al., 2006). In addition, glucocorticoids are a key to treating certain leukemias and are frequently included in chemotherapy regimens for their antiemetic, antiedema, and palliative properties. GR agonists are also the mainstay in the management of congenital adrenal hyperplasia and Addison's disease (adrenal insufficiency), in diagnostic tests for Cushing's syndrome (adrenal hyperfunction), and in certain psychiatric conditions. Furthermore, glucocorticoids are the treatment of choice for impending premature parturition to accelerate neonatal lung maturation. RU-486, a potent GR antagonist, causes generalized glucocorticoid resistance. In Cushing's syndrome caused by ectopic ACTH production or adrenal carcinoma, RU-486 can reverse the symptoms, ameliorate glucose intolerance, and normalize blood pressure. Multiple mechanisms contribute to the antagonistic actions of RU-486 with the GR (Rhen and Cidlowski, 2005). Binding of RU-486 with GR stabilizes the heat shock protein (HSP)-GR complex and alters the interaction of GR with coregulators, which together result in the formation of transcriptionally inactive GR molecules.

Prolonged glucocorticoid therapy causes serious side effects (Rhen and Cidlowski, 2005). Osteoporosis, metabolic syndrome, impaired development, and blunted growth all limit chronic use of glucocorticoids. Patients receiving long-term glucocorticoid treatment experience redistribution of body fat from the extremities to the trunk and face. Neural and psychological disturbances, such as psychosis, depression, and euphoria, can occur. To reduce these untoward actions of glucocorticoids, the lowest dosage with therapeutic efficacy, intermittent administration, and localized routes of administration have been implemented with some success (Buttgereit et al., 2005).

Dysregulation of the MR-aldosterone system reveals its importance in various human pathological conditions such as mineralocorticoid resistance, disorders of the CNS, hypertension, and cardiac failure (Katzung, 2004; Goodman et al., 2006). MR agonists such as fludrocortisone are used in the treatment of adrenal insufficiency. MR antagonists such as spironolactone and eplerenone are used for the treatment of hypertension, excess urine protein excretion, and heart failure. The potassium-sparing properties of spironolactone and eplerenone can be life-threatening if hyperkalemia develops (Sica, 2005).

The two most frequent uses of progestins are for contraception, either alone or with an estrogen in oral contraceptives, and for hormone replacement therapy when combined with estrogen in postmenopausal women (Katzung, 2004; Goodman et al., 2006). Progestins are also used in several settings for ovarian suppression, e.g., dysmenorrhea, endometriosis, hirsutism, and uterine bleeding. In addition, progesterone can be used diagnostically to test for estrogen secretion and for responsiveness of the endometrium. Progestins have been used as a palliative measure for metastatic endometrial carcinoma and in the treatment of renal and breast carcinoma. The presence of the PR is considered a useful prognostic marker in breast cancer irrespective of the patient's progestational status. Contraception with progestins is useful in patients with hepatic disease, hypertension, psychosis, or mental retardation. The side effects include headache, dizziness, weight gain, and glucose intolerance. Recent studies suggest that certain progestin plus estrogen replacement regimens in postmenopausal women may increase the incidence of breast cancer, a finding that may promote the development of improved hormone replacement therapy (Rossouw et al., 2002).

The GR antagonist RU-486 is also a potent PR antagonist. RU-486 binds to PR with high affinity and can terminate pregnancy (Schreiber and Creinin, 2005). RU-486 has effects on ovulation as well. If given acutely in the mid to late follicular phase of the menstrual cycle, RU-486 delays follicle maturation and the luteinizing hormone surge, and ovulation occurs later than normal. If the drug is given intermittently or continuously, ovulation is prevented in most but not all cases. These effects are largely due to actions on the hypothalamus and pituitary rather than the ovary. RU-486 may produce effects on the cervix, myometrium, ectopic endometrial tissue (i.e., endometriosis), certain types of breast cancer, and meningiomas via its antiprogestin activity. RU-486 has been used as a postcoital contraceptive, and it may be slightly more effective than high-dose estrogen-progestin combinations. The mechanism of action in this case is thought to be prevention of implantation. Other investigational or potential uses for RU-486 include the induction of labor after fetal death or at the end of the third trimester and treatment of endometriosis, leiomyoma, breast cancer, and meningioma. The antiprogestin activity of RU-486 is mediated by binding to the PR (Wardell and Edwards, 2005). Binding of RU-486 induces a conformational change in the PR LBD that facilitates the dissociation from heat shock protein complexes, dimerization of the receptor, and cooperative binding to hormone response elements in target genes (Gass et al., 1998). The distinct conformational changes in the receptor LBD induced by RU-486 inhibit coactivator recruitment but facilitate receptor interaction with corepressors including nuclear receptor corepressor (NCoR) and silencing mediator of retinoic acid and thyroid receptors (Wagner et al., 1998). RU-486 binding to PR also disrupts an intramolecular interaction between the N and C domains that has been shown to be required for maximal activity of the agonist-occupied receptor (Tetel et al., 1999). Detailed structure-function studies have also revealed that RU-486 binding may recruit RU-486-specific corepressors to specific residues in the receptor C-terminal tail (Vegeto et al., 1992; Xu et al., 1996). In addition, RU-486-bound receptors counteract agonist-bound receptors via formation of inactive het-

erodimers (Meyer et al., 1990; Leonhardt et al., 1998). Via these mechanisms, RU-486 acts as a potent antagonist for PR. RU-486 can also be a partial agonist for both PR and GR when selective coregulators are recruited (Jackson et al., 1997; Schulz et al., 2002). Other PR antagonists such as ZK 98299 have been developed. However, none of these compounds has been used extensively in the clinical setting because of toxicity.

Androgen therapy is primarily used in male hypogonadism, in aging, and in attempts to reverse protein loss after trauma, surgery, or prolonged immobilization (Katzung, 2004; Goodman et al., 2006). Androgens are also used in boys with delayed puberty, and the weak androgen danazol is used in women with endometriosis. The principal clinical application of AR antagonists such as flutamide, nilutamide, or bicalutamide is in the treatment of prostate cancer, usually in conjunction with long-acting luteinizing hormone-releasing hormone analogs. Androgen blockade usually decreases the volume of the primary and metastatic lesions by inducing apoptosis (Kyprianou et al., 1990). Despite the initial response to antiandrogen therapy, however, an androgen-refractory status with a fatal outcome frequently develops (Isaacs, 1999). Recurrent prostate cancer seems to result from increased AR signaling caused by increased AR expression in the presence or absence of AR gene amplifications (Koivisto et al., 1997), increased expression of enzymes that convert adrenal androgens to testosterone (Stanbrough et al., 2006), AR mutations (Tan et al., 1997; Taplin et al., 1999; Marcelli et al., 2000; Feldman and Feldman, 2001; Gregory et al., 2001), or AR activation in a ligand-independent manner (Craft et al., 1999). The onset of recurrent prostate cancer seems to involve increased AR-dependent growth factor signaling that overcomes apoptosis induced by androgen depletion (Ruijter et al., 1999; Feldman and Feldman, 2001). The aim of continued research in this area is to improve the prognosis for patients with prostate cancer.

Adverse effects of androgen treatment in women include hirsutism, acne, amenorrhea, clitoral enlargement, and deepening of the voice (Katzung, 2004; Goodman et al., 2006). Androgen replacement or performance-enhancing steroid use in men may cause sleep apnea, polycythemia, azoospermia, a decrease in testicular size, aggression, and psychosis. On the other hand, androgen blockade used in treating prostate cancer can be accompanied by hot flushes, loss of libido and sexual potency, and bone loss and osteoporosis (Labrie et al., 2004).

Prospectus

In 1849, Berthold showed that the transplantation of gonads into castrated roosters prevents the typical signs of castration and published the first experimental evidence for the effect of an endocrine gland (Klein, 1968).

More than a century later, the first steroid receptor was cloned (Hollenberg et al., 1985). In the past 20 years, tremendous progress has been made in our understanding of the fundamental mechanisms of the intracellular steroid hormone receptors. Continued effort by researchers in the field is paving the way for more efficient and specific therapeutic approaches via modulation of the GR, MR, PR, and AR. Although each of these receptors is encoded by a single gene, recent evidence suggests that multiple GR, MR, and PR receptor isoforms are produced (Kastner et al., 1990; Pascual-Le Tallec et al., 2004; Lu and Cidlowski, 2005). Via both transcriptional and translational mechanisms, the GR gene, for instance, produces a minimum of 16 GR proteins with distinct functions and tissue distribution patterns (Lu and Cidlowski, 2005). These receptor isoforms increase the number of molecular targets underlying diseases. In addition, alternative signaling pathways of steroid hormone receptors are being investigated. The ability of the GR to change the half-lives of certain mRNAs, notably via interaction with specific signals in the untranslated regions, has been recognized as a potentially important anti-inflammatory mechanism (Mozo et al., 1998; Newton et al., 1998). Steroid receptors localized on cell membranes, such as the PR on spermatozoa, can also trigger multiple signaling pathways to affect cell function (Gadkar-Sable et al., 2005). Another important aspect of continuing research is the development of selective modulators of these receptors that are capable of maintaining the beneficial responses mediated by each receptor while reducing unwanted side effects (Chang and McDonnell, 2005). For example, an ideal selective GR modulator would have therapeutic actions in specific tissues or would have the ability to dissociate transactivation and transrepression effects of GR, an ideal selective PR modulator would have antiproliferative effects on the endometrium and breast but would not oppose the protective effects of estrogen on bones and the cardiovascular system (Smith and O'Malley, 2004; Chwalisz et al., 2005), and selective AR modulators could be effective therapies in treating prostate cancer. Thus, exciting new avenues are being discovered by studies of the classic steroid hormone receptors.

Tables 1 through 4 summarize the functions, biologic activities, structural properties, and ligands of GR, MR, PR, and AR, respectively.

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TABLE 1
GR

Receptor nomenclature	NR3C1
Receptor code	4.10.1:GC:3:C1
Other names	GCCR, GCR, GRL
Molecular information	Hs: 777aa, P04150, chr. 5q31-q32[1]
	Rn: 795aa, P06536, chr. 18p12[2]
	Mm: 783aa, P06537, chr. 18 B3[3]
DNA binding	
Structure	Homodimer
HRE core sequence	GGTACANNNTGTTCT (GRE, half-site, palindrome)
Partners	HSP90 (physical, functional): cellular localization[4–6]; HMGB (physical, functional): DNA binding[7,8]; AP-1 (physical, functional): transactivation[9–11]; NF-κB (physical, functional): transactivation[12,13]; 14-3-3σ (physical, functional): cellular localization, transactivation[14]
Agonists	Dexamethasone (1–8 nM),* triamcinolone acetonide (6 nM),* prednisolone (15 nM), triamcinolone (20 nM), cortisol (10–50 nM),* corticosterone (60 nM),* desoxycorticosterone (70 nM) [IC_{50}][15–19]
Antagonists	RU-486 (0.4 nM)* [K_d][15,20]
Coactivator	CREBBP, NCOA2, MTI-II, NCOA6, PPARBP[22–27]
Corepressor	BAG1[28]
Biologically important isoforms	GRα {Hs, Mm, Rn}: main isoform[1]; GRβ {Hs}: widely expressed alternative splicing variant lacking ligand binding, associated with several diseases[1,29]; GR-A, B, C, D {Hs, Mm, Rn}: alternative translation initiation isoforms with distinct transcriptional activities and tissue distribution patterns[30]
Tissue distribution	Ubiquitous {Hs, Mm, Rn} [Northern blot, Q-PCR, in situ hybridization, Western blot][1,30–33]
Functional assay	Suppression of endogenous cortisol level by exogenous dexamethasone {Hs}[34]; apoptosis of thymocytes in the thymus {Rn}[35]; elevated blood glucose level by intravenous injection of glucocorticoids {Hs}[36,37]
Main target genes	Activated: PEPCK-C {Hs},[38] MKP-1 {Mm},[39] lipocortin-1 {Hs},[40,41]; repressed: PEPCK-C {Hs},[38] IL-8 {Hs},[42] TNF-α {Hs}[43]
Mutant phenotype	GR$^{-/-}$ mice die within hours because of respiratory failure; they have atelectatic lungs, impaired liver function, impaired HPA axis, increased plasma levels of ACTH and corticosterone and enlarged adrenal glands that produce no adrenaline {Mm} [knockout][44,45]; mice expressing type II GR antisense RNA exhibit impaired T-cell function, disrupted HPA axis, increased plasma levels of ACTH and corticosterone, reduced GR binding, and alterations in thymocyte migration {Mm} [antisense oligonucleotide][46]
Human disease	Glucocorticoid resistance: due to various SNPs[47,48]; glucocorticoid hypersensitivity: due to an N363 polymorphism[49]; asthma: due to a receptor mutation[50,51]; acute childhood lymphoblastic leukemia: due to a receptor mutation[52]

aa, amino acids; chr., chromosome; HRE, hormone response element; RXR, retinoid X receptor; HMGB, chromosomal high-mobility group B; NK-κ B, nuclear factor-κ B; PPARBP, peroxisome proliferator-activated receptor binding protein; Q-PCR, quantitative polymerase chain reaction; HPA, hypothalamo-pituitary-adrenal; ACTH, adrenocorticotropin; SNP, single-nucleotide polymorphism; GRE, glucocorticoid response element; CREBBP, cAMP response element binding protein binding protein.
* Radioligand.

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TABLE 2
MR

Receptor nomenclature	NR3C2
Receptor code	4.10.1:MC:3:C2
Other names	MR, MCR, MLR, aldosterone receptor
Molecular information	Hs: 984aa, P08235, chr. 4q31.1[1] Rn: 981aa, P22199, chr. 19q11[2] Mm: 978aa, Q8VII8, chr. 8 C1[3]
DNA binding	
Structure	Homodimer, heterodimer
HRE core sequence	ACAAGANNNTGTTCT (GRE, half-site, palindrome)
Partners	HSP90 (physical, functional): cellular localization[4]; HMGB (physical, functional): DNA binding[5,6]; 11β-HSD2 (functional): tissue specificity[7]
Agonists	Desoxycorticosterone (1×10^{-11} M), progesterone (1×10^{-11} M),* fludrocortisone (1.2×10^{-10} M), cortisol (1.1–1.5×10^{-10} M), dexamethasone (1×10^{-9} M)* [IC$_{50}$][8,9]; aldosterone (1–1.5×10^{-10})* [K_{d}][8,9]
Antagonists	Drospirenone ($<1 \times 10^{-10}$ M), spironolactone (1.4×10^{-8} M), eplerenone (1×10^{-7} M) [IC$_{50}$][8,10–12]
Coactivator	NCOA1, PGC-1α, ELL[13–15]
Corepressor	NCOR1, NCOR2, PIAS1[16,17]
Biologically important isoforms	MR-A {Hs, Mm, Rn}: main isoform[18]; MR-B {Hs, Mm, Rn}: truncated N terminus[18]; various splice variants also exist resulting in either altered DNA or ligand binding {Hs, Rn}[19–21]
Tissue distribution	Liver, brain, heart, kidney, colon, aorta, hippocampus, hypothalamus, adrenal fasciculate, epidermal keratinocytes, neurons of the CNS, cardiac myocytes, endothelial and smooth muscle cells of the vasculature {Hs,Mm,Rn} [Northern blot, Q-PCR, in situ hybridization, Western blot, immunohistology][22–33]
Functional assay	Renal clearance {Mm}[34]; colonic transepithelial Na$^+$ reabsorption {Mm}[34,35]
Main target genes	Activated: Enac {Hs},[36,37] SGK1{Rn},[38–40] GILZ{Rn}[41]
Mutant phenotype	Homozygous MR-deficient mice have a normal prenatal development; during the 1st week of life, these animals develop symptoms of pseudohypoaldosteronism, lose weight, and eventually die at around day 10 due to kidney failure {Mm} [knockout][34]; a conditional knockout model expressing solely in the heart an antisense mRNA directed against the murine MR; within 2–3 months, mice develop severe heart failure in the absence of hypertension or chronic hyperaldosteronism {Mm} [antisense oligonucleotide][3]
Human disease	Hypertension: Ser^{810} → Ile SNP causes gain of function[42]; pseudohypoaldosteronism type 1: various polymorphisms cause loss of activity; autosomal-dominant; haploinsufficiency seems to be the predominant mechanism[43,44]

aa, amino acids; chr., chromosome; HRE, hormone response element; ELL, eleven-nineteen lysine-rich leukemia; HMGB, chromosomal high-mobility group B; 11β-HSD2, 11β-hydroxysteroid dehydrogenase 2; Q-PCR, quantitative polymerase chain reaction; SNP, single-nucleotide polymorphism; GRE, glucocorticoid response element.
* Radioligand.

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TABLE 3
PR

Receptor nomenclature	NR3C3
Receptor code	4.10.1:PG:3:C3
Other names	PGR, progesterone receptor
Molecular information	Hs: 933aa, P06401, chr. 11q22[1]
	Rn: 923aa, Q63449, chr. 8q11[2]
	Mm: 923aa, Q00175, chr. 9 A1[3]
DNA binding	
Structure	Homodimer
HRE core sequence	GGTACANNNTGTTCT (GRE, palindrome)
Partners	HSP90 (physical): cellular localization[4,5]; HMGB (physical, functional): DNA binding[6,7]
	Src family kinases (physical): activation of rapid signalling cascades, independent of PR DNA binding[8]
Agonists	Levonorgestrel, medroxyprogesterone,* promegestone (R5020),* dydrogesterone, norethisterone, progesterone (P4)[9]
Antagonists	Asoprisnil, mifepristone (RU486),* RTI 3021-012, RTI 3021-022, onapristone (ZK98299)
Coactivator	NCOA1, NCOA3, CREBBP, SRA1, JDP2[10–20]
Corepressor	NCOR2[21–24]
Biologically important isoform	PRA {Hs, Mm, Rn}: N-terminally truncated isoform that is a weak transcriptional activator of specific target genes in a cell type-dependent manner and a strong repressor of transactivation by PRB and other steroid receptors[25,26]; PRB{Hs}: full-length protein that strongly activates target genes[27]
Tissue distribution	Mammary gland, uterus, brain, muscle, testis, ovary {Hs, Mm, Rn} [Northern blot, in situ hybridization, Western blot, immunohistology][28,29]
Functional assay	Inhibition of proliferation in endometrial cells caused by treatment of ovariectomized (estrogen-treated) mice with progesterone{Mm}[30,31]; proliferation in PR-positive breast cancer cells and normal breast epithelial cells{Hs}[32,33]; mammary gland ductal tree branching and lobuloalveolar development in ovariectomized (estrogen-treated) mice treated with progesterone{Mm}[34,35]
Main target genes	Activated: FSHβ,[36] multidrug resistance 1B{Mm},[37] Stat5A{Hs},[38] 11β-hydroxysteroid dehydrogenase{Hs},[38] Indian hedgehog{Mm}[39]
Mutant phenotype	Disruption of both PRA and B isoforms results in impaired sexual behavior, anovulation, uterine dysfunction, and reduced ductal branching and lobuloalveolar development in the mammary gland {Mm} [knockout][40]; targeted overexpression of PRA in the mammary gland results in reduced induction of apoptosis {Mm} [overexpression][41]
Human disease	Pseudocorpus luteum insufficiency: due to decreased PR expression[42]; breast cancer: higher PRA/PRB ratio correlates with increased tumor grade[43]; endometriosis: due to reduced expression of PRB (not PRA) in diseased tissue[44,45]; endometrial cancer: increased risk caused by polymorphisms in the PR promoter favoring expression of PRB[46,47]

aa, amino acids; chr., chromosome; HRE, hormone response element; HMGB, chromosomal high mobility group B; Q-PCR, quantitative polymerase chain reaction; GRE, glucocorticoid response element; CREBBP, cAMP response element binding protein binding protein.

* Radioligand.

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TABLE 4
AR

Receptor nomenclature	NR2B1
Receptor code	4.10.1:AG:3:C4
Other names	AIS, DHTR, dihydrotestosterone receptor, HUMARA, KD, NR3C4, SBMA, SMAX1, TFM
Molecular information	Hs: 919aa, P10275, chr. Xq11[1,2]
	Rn: 902aa, P15207, chr. Xq22[3]
	Mm: 899aa, P19091, chr. X C3[4–6]
DNA binding	
Structure	Homodimer
HRE core sequence	GGTACANNNTGTTCT (GRE, palindrome)
Partners	HSP90 (physical): cellular localization, specify protein stability[7,8]; HMGB (physical, functional): DNA binding[9,10]
Agonists	Mibolerone (1.65 nM),* DHT (2.23 nM), androstenedione (2.75 nM), methyltrienolone (3.07 nM),* testosterone (15.9 nM)* [IC_{50}][2]
Fluoxymesterone	
Antagonists	Hydroxyflutamide, bicalutamide, nilutamide, mifepristone, cyproterone acetate
Coactivators	RNF14, NCOA2, NCOA4, Fhl2, TGFB1I1, RAN[11–24]
Biologically important isoforms	AR-A {Hs}:187aa truncated from the N terminus[25–28]; AR-B {Hs}: 110 kDa[25–28]
Tissue distribution	Bone marrow, mammary gland, muscle, prostate, stem cells, testes, preputial gland, scrotal skin, vagina {Rn} [Western blot][29]
Functional assay	Treatment of castrated rats with AR ligands possessing anabolic activity results in increased skeletal muscle mass {Rn}[30]; androgen treatment causes increased expression of sex hormone-binding globulin in the hepatocarcinoma cell line HepG2 {Hs}[31]; treatment of castrated rats with AR ligands possessing anabolic activity results in increased weight of prostate and seminal vesicles {Rn}[30]
Main target genes	Activated: PSA {Hs, Rn, Mm},[32,33] probasin {Rn},[34] Slp {Mm},[35] prostatein C3 {Rn},[36] SC {Hs}[37,38]
Mutant phenotype	Male mice lacking AR$^{-/-}$ exhibit insulin resistance and impaired glucose tolerance {Mm} [knockout][39–41]; male mice lacking AR in Sertoli cells exhibit infertility with defective spermatogenesis and hypotestosteronemia {Mm} [knockout][42]
Human disease	Prostate cancer: mutations of AR affecting ligand binding as well as gene amplification of AR have been described[43]; androgen insensitivity syndrome: mutations of AR affecting ligand binding, DNA binding or nuclear localization[44,45]; Kennedy's disease (poly-Q): spinobulbar muscular atrophy is an X-linked form of motor neuron disease characterized by progressive atrophy of the muscles, dysphagia, dysarthria, and mild androgen insensitivity caused by CAG repeat expansion in the AR gene[46–48]; Klinefelter's syndrome (47, XXY, hypogonadism): characterized by undeveloped testes and sterility, skewed inactivation of the X-chromosome seems to contribute to reduced AR expression[49,50]

aa, amino acids; chr., chromosome; HRE, hormone response element; DHT, dihydrotestosterone; GRE, glucocorticoid response element.
* Radioligand.

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