

Nuclear Receptors (Steroids)

Key References

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Overview

Intracellular receptors (IRs) are a class of ligand-dependent transcription factors that include receptors for both steroid and non-steroid hormones. Upon binding their cognate hormone, these receptors homo- or hetero-dimerize and regulate gene expression through multiple mechanisms. Ligand-bound IRs can positively regulate transcription after binding to sequences within promoters containing binding sites for that IR; negative regulation can occur by direct binding to a promoter or indirectly by binding to and altering the activity of another transcription factor. It is now clear that accessory coactivator and corepressor proteins interact directly or indirectly with IRs play a key role in transcriptional regulation. These proteins, associate with the IR and influence chromatin organization and/or recruitment of basal transcription factors and RNA polymerase II. The pattern of genes modulated within a cell in response to an IR Ligand determines the ultimate effects on cell proliferation, cell differentiation and general cellular homeostasis.

Steroid receptors include receptors for glucocorticoids, progestins, estrogens, androgens and mineralocorticoids. While these receptors were demonstrated to exist within cells as early as the 1960s, it was not until 1984 that the first IR, the rat glucocorticoid receptor, was cloned and characterized. Since that time, the genes for all known human steroid IRs have been cloned.

Glucocorticoids are secreted from the adrenal cortex in response to adrenocorticotrophic hormone (ACTH). Glucocorticoids are primarily responsible for regulating carbohydrate, lipid and protein metabolism, cardiovascular function and the immune system. In response to stress,

the levels of endogenous corticosteroids can rise ten-fold. Therapeutically, synthetic corticosteroids including prednisone and dexamethasone are primarily used for their anti-inflammatory and immunoregulatory effects to treat both acute inflammatory responses, such as asthma, as well as chronic inflammatory diseases, such as rheumatoid arthritis. They are also used in various cancer chemotherapeutic regimens as a palliative treatment and for certain lymphoid malignancies because of their ability to induce apoptosis in specific immune cells.

Aldosterone, the major mineralocorticoid, is secreted from the adrenal gland and possibly other tissues. Aldosterone functions to maintain water and electrolyte balance by acting upon the distal tubules and collecting ducts of the kidney. Aldosterone antagonists, such as spironolactone, are potassium-sparing diuretics used for the treatment of hypertension. Spironolactone also shows significant benefit in the treatment of congestive heart failure.

Progesterone and other progestins are secreted by the corpus luteum during the menstrual cycle and play a key role in the early maintenance of the endometrial lining during pregnancy. Progestins, alone or in combination with estrogens, are used as oral contraceptives. Progestin antagonists, such as mifepristone (RU 486), can be used early in pregnancy as abortifacients.

Estrogens are synthesized by the ovaries in premenopausal women. Estrogens function to maintain secondary sexual characteristics and bone integrity in women. After menopause, estrogen replacement reduces hot flashes and prevents significant bone loss. The estrogen receptor partial agonist,

tamoxifen, is widely used in treating breast cancer. The partial agonist raloxifene is also an antagonist in the breast and an agonist for bone, but lacks the uterotrophic activity of tamoxifen. The molecular basis for these differences upon selective cofactor recruitment by ER bound to these selective ER modulators. In addition, aromatase inhibitors, which prevent the conversion of androgens to estrogen (e.g. anastrozole, letrozole, and exemestane) are also used to treat ER-positive breast cancer.

Testosterone, dihydrotestosterone and other androgens are responsible for behavioral and secondary sexual characteristics of both males and females. Testosterone, synthesized *de novo* by the testes and adrenal gland, is secreted during gestation, again during the neonatal period, and throughout adulthood. Testosterone functions to support sexual differentiation, spermatogenesis and has significant anabolic effects on muscle and bone. Antagonists of testosterone are used to treat prostate cancer. Inhibitors of the conversion of testosterone to dihydrotestosterone have been used to treat benign prostatic hypertrophy and may reverse male pattern baldness.

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CURRENTLY ACCEPTED NAME	Estrogen receptor	Glucocorticoid receptor	Progesterone receptor	Androgen receptor	Mineralocorticoid receptor
ALTERNATE NAME	ER α (NR3A1) ER β (NR3A2)	GR (NR3C1) GR α ^a	PR β (NR3C3) PR α ^d	AR (NR3C4)	MR (NR3C2)
STRUCTURAL INFORMATION	595 aa (human)	777 aa (human)	933 aa (human)	919 aa (human)	984 aa (human)
RECEPTOR SELECTIVE AGONISTS	17- β -Estradiol (E8875) Estrone (E9750) Moxestrol	Dexamethasone (D1756) Triamcinolone (T6376) Hydrocortisone (H4001) Prednisone (P6254)	Progesterone (P0130) Norethynodrel (N7253) Medroxyprogesterone (M1629) R5020 Iodovinylnortestosterone	Testosterone (T1500) Stanolone (A8380) Oxymetholone (O0380) Oxandrolone Methyltrienolone Fluoxymesterone (F7751) Androstenedione (A9630)	Aldosterone (A6628)
RECEPTOR SELECTIVE ANTAGONISTS	ICI 182,780 Keoxifene (R1402) 4-Hydroxytamoxifen ^b (H7904, H6278) Tamoxifen (T5648, T9262)	Mifepristone (RU 486) ^c (M8046) Onapristone (ZK 98299) ^c ZK 91587	Mifepristone (RU 486) (M8046) ^c Onapristone (ZK 98299) ^c	Bicalutamide 2-Hydroxyflutamide ^e Nilutamide (N8534) Cyproterone acetate (C3412) ^f	Spironolactone (S3378) Eplerenone
SIGNAL TRANSDUCTION MECHANISMS	Modulation of gene expression by ligand-dependent transcription factors				
RADIOLIGANDS OF CHOICE	[³ H]-Estradiol [¹²⁵ I]-Iodoestradiol [³ H]-Tamoxifen	[³ H]-Hydroxycortisone [³ H]-Deoxycorticosterone [³ H]-Dexamethasone	[¹²⁵ I]-Iodovinylnortestosterone [³ H]-Progesterone [³ H]-R5020	[³ H]-Dihydrotestosterone [³ H]-Methyltrienolone [³ H]-Testosterone	[³ H]-Aldosterone [³ H]-Spironolactone
TISSUE EXPRESSION	Ovary, pituitary, uterus	Ubiquitous	Uterus, brain, hypothalamus, ovary, spinal cord	Adrenal, brain, epididymus, hypothalamus, kidney, muscle, ovary, pituitary, prostate, skin, uterus, adipose tissue	Brain, colon, kidney, pituitary, skin, spinal cord, thyroid, heart
PHYSIOLOGICAL FUNCTION	Maintenance of female reproductive system	Regulation of carbohydrate, lipid, and protein metabolism and cardiovascular and immune function	Establishment and maintenance of pregnancy, breast development, sexual behavior	Proper development and function of male reproductive organs and anabolic action	Regulation of electrolyte and fluid balance and specific CNS roles
DISEASE RELEVANCE	Osteoporosis, cancer, pregnancy prevention	Asthma, arthritis, cancer	Pregnancy prevention and termination	Prostate cancer, osteoporosis, frailty	Congestive heart failure, blood pressure

Abbreviations

ICI 182,780: 7 α -[9-(4,4,5,5,5-Pentafluoro-pentylsulphinylnonyl)oestra-1,3,5(10)-triene-3,17 β -diol

R5020: 17,21-Dimethyl-19-nor-4,9-pregnadiene-3,20-dione

FOOTNOTES

a A second GR isoform (GR β) has been identified. GR β contains 742 amino acids, does not bind glucocorticoids and has been shown to be a dominant-negative mutant.

b Tissue-specific antagonist.

c Potent antiglucocorticoid and antiprogesterin with weaker potency as an antagonist on the androgen receptor.

d PR α and PR β are identical except for alternate splicing of amino terminal. PR β is approximately 22 kDa larger. The pharmacological differences are not fully understood.

e Active metabolite of flutamide.

f Also a progesterone agonist.