

## Intracellular 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 DNA binding sites for that IR; negative regulation can occur directly after binding to a promoter or indirectly by down-regulating the activity of other transcription factors. Recent studies have demonstrated a key role for accessory proteins that interact directly or indirectly with IRs to regulate transcription. These factors, called corepressors and coactivators, 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 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 sequences of 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 certain 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. It may also play a role in enhancing tissue repair after injury. Aldosterone antagonists, such as spironolactone, are potassium-sparing diuretics used for the treatment of hypertension. They have also shown significant benefit in the treatment of congestive heart failure.


Progesterone and other progestins are secreted by the corpus luteum during the menstrual cycle. Steroidal progestins, alone or in combination with estrogens, are used as oral contraceptives. Progestins play a critical role in the early maintenance of the endometrial lining during pregnancy. 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 yields significant therapeutic benefit. The most commonly prescribed drug in the United States is Premarin, a mixture of estrogens derived from pregnant mare urine. Estrogen receptor antagonists, such as tamoxifen, are widely used in treating breast cancer.

Testosterone, dihydrotestosterone and other androgens are responsible for secondary sexual and behavioral characteristics of males, and, with regards to behavior, to a lesser extent, of females. Testosterone, synthesized 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.

## Intracellular Receptors (Steroids)

CURRENTLY ACCEPTED NAME	Estrogen receptor	Glucocorticoid receptor	Progesterone receptor	Androgen receptor	Mineralocorticoid receptor
ALTERNATE NAME	ER $\alpha$ (NR3A1) ER $\beta$ (NR3A2)	GR (NR3C1) GR $\alpha$ <sup>a</sup>	PR $\beta$ (NR3C3) PR $\alpha$ <sup>d</sup>	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- $\beta$ -Estradiol ( <a href="#">E 8875</a> ) Estrone ( <a href="#">E 9750</a> ) Moxestrol	Dexamethasone ( <a href="#">D 1756</a> ) Triamcinolone ( <a href="#">T 6376</a> ) Hydrocortisone ( <a href="#">H 4001</a> ) Prednisone ( <a href="#">P 6254</a> )	Progesterone ( <a href="#">P 0130</a> ) Norethynodrel ( <a href="#">N 7253</a> ) Medroxyprogesterone ( <a href="#">M 1629</a> ) R5020 Iodovinylnortestosterone	Testosterone ( <a href="#">T 1500</a> ) Stanolone ( <a href="#">A 8380</a> ) Oxymetholone ( <a href="#">O 0380</a> ) Oxandrolone Methyltrienolone Fluoxymesterone ( <a href="#">F 7751</a> ) Androstenedione ( <a href="#">A 9630</a> )	Aldosterone ( <a href="#">A 6628</a> )
RECEPTOR SELECTIVE ANTAGONISTS	ICI 182,780 Keoxifene 4-Hydroxytamoxifen <sup>b</sup> ( <a href="#">H 7904</a> , <a href="#">H 6278</a> ) Tamoxifen ( <a href="#">T 9262</a> )	Mifepristone (RU 486) <sup>c</sup> ( <a href="#">M 8046</a> ) Onapristone (ZK 98299) <sup>c</sup> ZK 91587	Mifepristone (RU 486) ( <a href="#">M 8046</a> ) <sup>c</sup> Onapristone (ZK 98299) <sup>c</sup>	Bicalutamide 2-Hydroxyflutamide <sup>e</sup> Nilutamide Cyproterone acetate ( <a href="#">C 3412</a> ) <sup>f</sup>	Spirolactone ( <a href="#">S 3378</a> ) Eplerenone
SIGNAL TRANSDUCTION MECHANISMS	Modulation of gene expression by ligand-dependent transcription factors 				
RADIOLIGANDS OF CHOICE	[ <sup>3</sup> H]-Estradiol [ <sup>125</sup> I]-Iodoestradiol [ <sup>3</sup> H]-Tamoxifen	[ <sup>3</sup> H]-Hydroxycortisone [ <sup>3</sup> H]-Deoxycorticosterone [ <sup>3</sup> H]-Dexamethasone	[ <sup>125</sup> I]-Iodovinylnortestosterone [ <sup>3</sup> H]-Progesterone [ <sup>3</sup> H]-R5020	[ <sup>3</sup> H]-Dihydrotestosterone [ <sup>3</sup> H]-Methyltrienolone [ <sup>3</sup> H]-Testosterone	[ <sup>3</sup> H]-Aldosterone [ <sup>3</sup> H]-Spirolactone

### ABBREVIATIONS

**ICI 182,780:** 7 $\alpha$ -[9-(4,4,5,5,5-Pentafluoro-pentylsulphonyl)nonyl]oestra-1,3,5(10)-triene-3,17 $\beta$ -diol  
**R5020:** 17,21-Dimethyl-19-nor-4,9-pregnadiene-3,20-dione

### FOOTNOTES

- a** A second GR isoform (GR $\beta$ ) has been identified. GR $\beta$  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 antiprogestin with weaker potency as an antagonist on the androgen receptor.  
**d** PR $\alpha$  and PR $\beta$  are identical except for alternate splicing of amino terminal. PR $\beta$  is approximately 22 kDa larger. The pharmacological differences are not fully understood.  
**e** Active metabolite of flutamide.  
**f** Also a progesterone agonist.