http://aris.gusc.lv/06Daugavpils/Research/NuclearReceptor.pdf

NUCLEAR RECEPTORS NR 2019 Member

Subfamily		Group NRNC		Symbol[6]	Abbreviation	Name	Gene	lipophilic Ligand(s)
1	Thyroid Hormone Receptor-like	A	Thyroid hormone receptor	NR1A1	TRα	receptor-α	*THRA*	thyroid hormone
				NR1A2	TRβ	receptor-β	*THRB*	
		B	Retinoic acid receptor	NR1B1	RARα	receptor-α	*RARA*	vitamin A and related compounds
				NR1B2	RARβ	receptor-β	*RARB*	
				NR1B3	RARγ	receptor-γ	*RARG*	
		C	**Peroxisome proliferator-activated receptor**	NR1C1	PPARα	receptor-α	*PPARA*	**fatty acids**, **prostaglandins**
				NR1C2	PPAR-β/δ	receptor-β/δ	*PPARD*	
				NR1C3	**PPARγ**	**receptor-γ**	***PPARG***	
		D	Rev-ErbA	NR1D1	Rev-ErbAα	Rev-ErbAα	*NR1D1*	heme
				NR1D2	Rev-ErbAβ	Rev-ErbAα	*NR1D2*	
		F	RAR-related orphan receptor	NR1F1	RORα	orphan receptor-α	*RORA*	**cholesterol**, ATRA
				NR1F2	RORβ	orphan receptor-β	*RORB*	
				NR1F3	RORγ	orphan receptor-γ	*RORC*	
		H	Liver X receptor-like	NR1H3	LXRα	Liver X receptor-α	*NR1H3*	oxysterols
				NR1H2	LXRβ	Liver X receptor-β	*NR1H2*	
				NR1H4	FXR	Farnesoid X receptor	*NR1H4*	
		I	Vitamin D receptor-like	NR1I1	VDR	D receptor	*VDR*	vitamin D
				NR1I2	PXR	Pregnane X receptor	*NR1I2*	xenobiotics
				NR1I3	CAR	receptor	*NR1I3*	androstane
		X	NRs with two DNA binding domains[35][36]	NR1X1	2DBD-NRα			
				NR1X2	2DBD-NRβ			
				NR1X3	2DBD-NRγ			

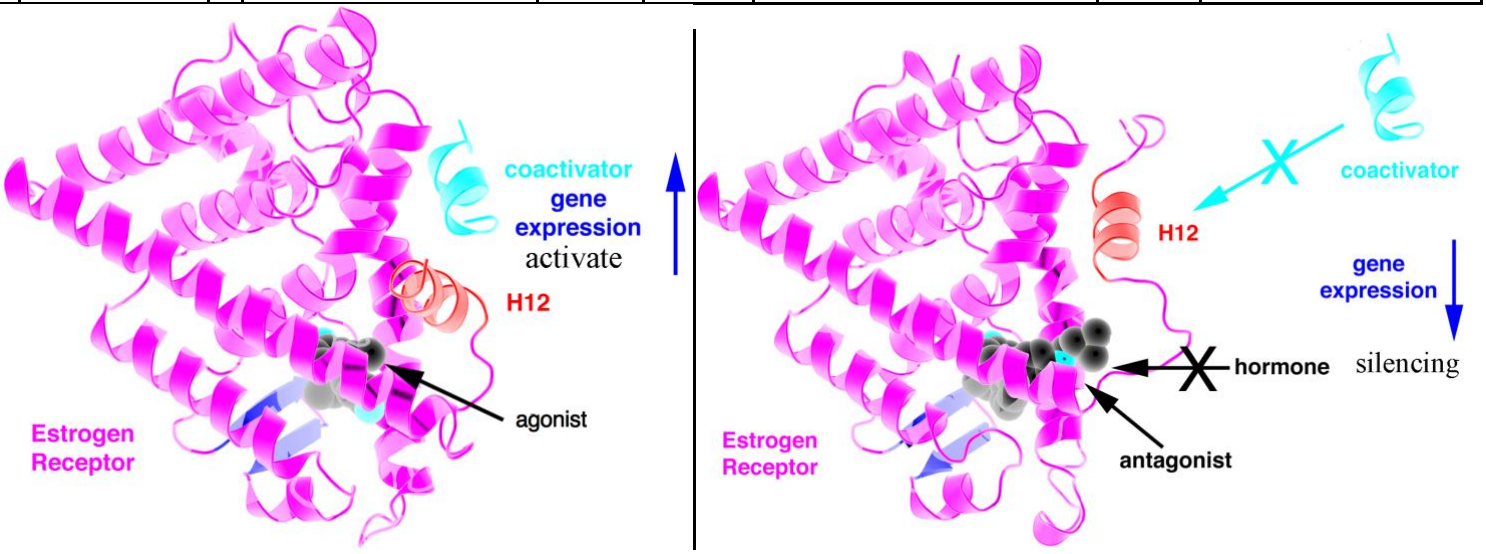
Nuclear receptors NRs are a major transcription factor family whose members selectively bind small-molecule **lipophilic ligands** and transduce those signals into specific changes in **gene programs**. **HETERO-DIMER RXRα** + **PPARγ** ; each MONOMER have 1)Ligand-Binding Domains **LBD**s;2) DNA-Binding Domains **DBD**

2	Retinoid X Receptor-like	A	Hepatocyte nuclear factor-4	NR2A1	HNF4α	nuclear factor-4-α	*HNF4A*	fatty acids
				NR2A2	HNF4γ	nuclear factor-4-γ	*HNF4G*	
		B	**Retinoid X receptor**	**NR2B1**	**RXRα**	**receptor-α**	***RXRA***	**retinoids**
				NR2B2	RXRβ	receptor-β	*RXRB*	
				NR2B3	RXRγ	receptor-γ	*RXRG*	
		C	Testicular receptor	NR2C1	TR2	receptor 2	*NR2C1*	
				NR2C2	TR4	receptor 4	*NR2C2*	
		E	TLX/PNR	NR2E1	TLX	Drosophila tailless gene	*NR2E1*	Homologue of the
				NR2E3	PNR	nuclear receptor	*NR2E3*	Photoreceptor cell-specific
		F	COUP/EAR	NR2F1	COUP-TFI	transcription factor I	*NR2F1*	Chicken ovalbumin upstream promoter-
				NR2F2	COUP-TFII	transcription factor II	*NR2F2*	Chicken ovalbumin upstream promoter-
				NR2F6	EAR-2	V-erbA-related	*NR2F6*	

A/B regions poorly conserved that in some cases act as potent transcriptional activators, provide sites of protein **phosphorylation** or form direct interactions with other receptor domains or regulatory proteins. Highly conserved **DBD** contains two zinc-binding sites capable of sequence-specific binding to **DNA**. **Hydrophobic** molecules bind to the **LBD**, repositioning **helix 12** into an active conformation recruits **co-regulators**. **Coactivators** members of the **steroid receptor coactivator SRC** contain LXXLL motifs that dock to **LBD**. **PPARγ LBD+DBD RXRα** enhance binding response-element **A**, **T**, **G**, **C** on DNA sequence. The **androgen receptor** (**AR**), also known as **NR3C4** (**nuclear receptor** subfamily 3, group C, member 4), is a type of **nuclear receptor**that is activated by binding of either of the androgenic hormones **testosterone** or**dihydrotestosterone** in the cytoplasm and then translocating into the nucleus.

3	Estrogen	A	Estrogen receptor	NR3A1	ERα	Estrogen receptor-α	*ESR1*	estrogens

	Receptor-like			NR3A2	ERβ	Estrogen receptor-β		
		B	Estrogen related receptor	NR3B1	ERRα	receptor-α	*ESR2*	Estrogen-related
				NR3B2	ERRβ	receptor-β	*ESRRA*	Estrogen-related
				NR3B3	ERRγ	receptor-γ	*ESRRB*	Estrogen-related
		C	3-Ketosteroid receptors	NR3C1	GR	receptor	*ESRRG*	Glucocorticoid
				NR3C2	MR	Mineralocorticoid receptor	*NR3C1*	cortisol
				NR3C3	PR	Progesterone receptor	*NR3C2*	aldosterone
				NR3C4	AR	Androgen receptor	*PGR*	progesterone, testosterone
4	Nerve Growth Factor IB-like	**A**	NGFIB/NURR1/NOR1	NR4A1	NGFIB	Nerve Growth factor IB	*AR*	testosterone
				NR4A2	NURR1	Nuclear receptor related 1	*NR4A1*	
				NR4A3	NOR1	Neuron-derived orphan receptor 1	*NR4A2*	
5	Steroidogenic Factor-like	**A**	SF1/LRH1	NR5A1	SF1	Steroidogenic factor 1	*NR4A3*	
				NR5A2	LRH-1	Liver receptor homolog-1	*NR5A1*	phosphatidylinositols
6	Germ Cell Nuclear Factor-like	**A**	GCNF	NR6A1	GCNF	Germ cell nuclear factor	*NR5A2*	phosphatidylinositols
0	Miscellaneous	**B**	DAX/SHP	NR0B1	DAX1	Dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1	*NR6A1*	
				NR0B2	SHP	Small heterodimer partner	*NR0B1*	*NR0B2*



Ligand bind **LBD** change conformation with **coactivator** helix **H12 NR** DNA binding domain :

1) for a**gonist** activate **gene** expression. Receptor+Hormone works.

2)for **antagonists gene** expression silencing no **coactivation** of **gene** expression.

Receptor is +busy + not working (silencing).

The **androgen receptor** (**AR**), also known as **NR3C4** (**nuclear receptor** subfamily 3, group C, member 4), is a type of **nuclear receptor**that is activated by binding of either of the androgenic hormones **testosterone** or**dihydrotestosterone** in the cytoplasm and then translocating into the nucleus. The **androgen receptor** is most closely related to the progesterone receptor, and progestins in higher dosages can block the **androgen receptor**. The main function of the **androgen receptor** is as a DNA-binding transcription factor that regulates gene expression; however, the **androgen receptor** has other functions as well. **Androgen** regulated genes are critical for the development and maintenance of the male sexual phenotype.

The crystal structure of a complete receptor in complex with its ligand and DNA-response element, however, has been solved only for the peroxisome proliferator-activated receptor γ (PPARγ)-retinoid X receptor α (RXRα) heterodimer. This structure provided the first indication of direct interactions between the DNA-binding domain (DBD) and ligand-binding domain (LBD). In this study, we investigated whether there is a similar interface between the DNA- and ligand-binding domains for the androgen receptor (AR). Nuclear receptors are multi-domain transcription factors that bind to DNA elements from which they regulate gene expression. The peroxisome proliferator-activated receptors (PPARs) form heterodimers with the retinoid X receptor (RXR), and PPAR-γ. PPAR-γ and RXR-α form a non-symmetric complex, allowing the ligand-binding domain (LBD) of PPAR-γ to contact multiple domains in both proteins. Three interfaces link PPAR-γ and RXR-α, including some that are DNA dependent. The PPAR-γ LBD cooperates with both DNA-binding domains (DBDs) to enhance response-element binding. The A/B segments are highly dynamic, lacking folded substructures despite their gene-activation properties.

I. hNR, human DNA nuclear receptor.

Nuclear receptors (NRs) are involved in many physiological processes, diseases, and therapeutic applications. They are transcription factors that contain a DNA-binding domain (DBD) composed of 2 zinc fingers (40) and a ligand-binding domain (LBD) formed by 12 a helices (60). The structures of the separate DNA-binding and ligand-binding domains of many receptors have already revealed a large amount of information. (NR DBD LBD) in complex with two natural androgens, testosterone (Testo TES, progesterone STR) and dihydrotestosterone (DHT), and with an androgenic steroid used in sport doping, tetrahydrogestrinone (THG, R1888 (17H)).
The hARLBD steroid-binding site together with TES,DHT,17H bound.

Athletes are constantly striving for better performance in their sports. Most athletes stay in top shape through a rigorous training program in fitness and nutrition, giving them the strength and stamina to push their bodies to the physical limit. But some athletes also look to biochemistry to improve their performance even further. There are many ways to give nature an artificial boost. For instance, some athletes artificially increase the number of red blood cells in their blood, either by injecting purified cells or by using the blood-stimulating hormone erythropoietin. The extra red blood..

Introduction Athletes are constantly striving for better performance in their sports. Most athletes stay in top shape through a rigorous training program in fitness and nutrition, giving them the strength and stamina to push their bodies to the physical limit. But some athletes also look to biochemistry to improve their performance even further. There are many ways to give nature an artificial boost. For instance, some athletes artificially increase the number of red blood cells in their blood, either by injecting purified cells or by using the blood-stimulating hormone erythropoietin. The extra red blood cells carry more oxygen to their straining muscles than in normal blood, giving them an edge in endurance. Similarly, many male athletes use steroid hormones like testosterone to spur their muscles into growth far beyond what is normally possible, giving them the edge in strength. These methods are controversial and regarded by many to be unethical, and thus are generally banned from organized sporting events. However, the many drug testing scandals currently in the news show that these methods are still in widespread use.

Making the Man Anabolic steroids like testosterone are among the most common performance enhancing drugs used by athletes today. Anabolic steroids have two major functions. First, they are *androgenic*, being responsible for control of "male" characteristics. Before birth, testosterone directs the formation of male characteristics in the growing embryo, and at puberty, raised levels of testosterone direct the changes as a boy grows into a man. Second, these steroids are *anabolic*: they regulate anabolic processes such as synthesis of protein in muscle, formation of blood cells, and the emotional and physical aspects of sexual function.

Testosterone Action Testosterone is produced naturally by the testes and circulates through the blood, acting on cells throughout the body. Much of this testosterone is transported inside carrier proteins in the blood, including **serum albumin** and sex hormone binding globulin **SHBG**, shown here from PDB entry **1D2S**. These carriers slowly release testosterone, which slips through cell membranes and into cells. Once inside, a cellular enzyme often converts it to an even more active form, 5-alpha-dihydrotestosterone . Then it finds its way to the nucleus, where it binds to the androgen receptor and changes the expression of a wide variety of genes, turning on various anabolic and androgenic functions.

Designer Steroids In the early 1960s, weightlifters and bodybuilders discovered that anabolic steroids improved their performance in aerobic and endurance sports. Testosterone was discovered earlier, in 1935, but it was quickly discovered that it could not be taken orally--it is rapidly removed from the blood by the liver. Instead, a variety of modified forms of testosterone, generally termed anabolic steroids, were developed that either mimic testosterone or are converted to testosterone in the body. Ever since then, these compounds have been used and

misused by amateur and professional athletes. In 1975, the International Olympic Committee placed steroids on their list of banned substances, and most professional sports organizations currently ban their use. This has led to a tug-of-war between ambitious athletes and regulatory officials, including things like "designer steroids" that are designed to be undetectable by current testing methods and random testing protocols that catch athletes who regularly take steroids but stop a few weeks before an event to be clean for a scheduled test.

Supplementing Performance Testosterone is created step-by-step by a collection of enzymes, starting from cholesterol. The enzyme shown here, 17-beta hydroxysteroid **DHT** dehydrogenase (PDB entry **1XF0**), performs the last step in this process, converting androstenedione into testosterone. In this picture, the androstenedione is shown in green and an NADP cofactor is shown in magenta. These enzymes provide the basis for several "dietary supplements" that have close connections to anabolic steroids. Until 2004 (when it was banned by the FDA), you could buy androstenedione as a supplement. It is converted to testosterone in the body, and shows about a tenth of the activity of testosterone. Dihydroepiandrostenone (DHEA), however, is still sold as a supplement. It is two metabolic steps away from testosterone, requiring the action of two enzymes to create the active form.
Exploring the Structure Once testosterone gets into cells, it binds to the androgen receptor and modifies the expression of many anabolic and androgenic genes. The androgen receptor is very similar to the estrogen receptor, with a domain that binds to the proper sequences of DNA and a domain that binds to testosterone. Because the molecule is rather flexible, these two domains have been studied separately by X-ray crystallography. You can look at the DNA binding domain in entry **1R4I**-3DZY, 1XQ3, 1XOW-it is pictured here. Two structures of the testosterone-binding domain are shown here: on the left (PDB entry **2AM9**) is one bound to testosterone and on the right (PDB entry **2AMB**) is a structure bound to a synthetic designer steroid, tetrahydrogestrinone (**THG**). **THG** is the "undetectable" anabolic steroid uncovered in the 2003 BALCO doping scandal. **1R4I**

The androgen receptor (AR) is a member of the nuclear receptor (NR) superfamily (Mangelsdorf et al. 1995). Like the other NRs, it is constituted by three main functional domains: a variable N-terminal domain (NTD), a highly conserved DNA-binding domain (DBD), and a conserved ligand-binding domain (LBD) (Jenster et al. 1991).

After binding of an androgen to its LBD, AR rapidly translocates to the nucleus, where it directly interacts with DNA as a homodimer, at androgen response elements (ARE) found in the regulatory regions of target genes. This complex can thenceforth recruit coactivators (Jenster 1998) through the ligand-dependent transactivation function (AF-2) located in the LBD and hence control transcription of specific genes. Through this mechanism, androgens such as testosterone (Testo TES) and 5a-dihydrotestosterone (DHT) regulate a wide range of physiological responses, most notably male sexual differentiation and maturation including the development, growth, and maintenance of the normal prostate (Mooradian et al. 1987; Keller et al. 1996; Roy et al. 1999).

Defects in AR function are involved in health disorders including prostate cancer's resistance to androgen ablation therapy (this case unemploiable therapy) (Quigley et al. 1995; Heinlein and Chang 2004). Because of their anabolic characteristics, androgens have been used by athletes for a long time (Evans 2004). It is thus not surprising that chemically modified androgens, often synthesized for pharmacological purposes, have rapidly given rise to interest in elite sports. Indeed, athletes have been using modified steroids with a higher anabolic:androgenic ratio to enhance their performances. Recently, a novel chemically modified steroid, tetrahydrogestrinone (THG), has appeared as a doping agent. A potent androgen and progestin (Death et al.2004), THG is produced by the hydrogenation of gestrinone, a progestin used to treat endometriosis (Dawood et al. 1997), and has been identified as the first true “designer androgen,” being custom produced to evade detection (Catlin et al. 2004). Indeed, it was undetectable in urine by standard antidoping tests until Catlin et al. (2004) developed a specific test. Using a pangenomic assay, THG has been shown to modulate hundreds of genes in a time-dependent fashion almost superimposable to DHT (Labrie et al. 2005). All androgens, natural or chemically designed, exert their action via the AR by binding its unique LBD. However, these various ligands bind AR with very different affinities, their Ki values ranging from low nanomolar concentrations for the most potent androgens to micromolar concentrations for the weaker ones.

The PPARs, like many non-steroid members of the nuclear receptor family, function as obligate heterodimers with RXR13. PPAR-a, PPAR-ß/d and PPAR-? are encoded separately, but have overlapping tissue expression patterns, and as a group coordinate the regulation of important metabolic pathways 2,14,15. These receptors control cellular processes including regulation of lipid and carbohydrate metabolism. PPAR-?, the best-studied member of the family, is expressed in both white and brown adipocytes and regulates adipocyte differentiation, lipid storage and release 16. One class of PPAR-? ligands, the thiazolidinediones, which includes the drug rosiglitazone, are effective insulin sensitizers, and have been shown to improve glucose uptake and lower hyperglycaemia and hyperinsulinaemia 17–20. The PPARs are also potential therapeutic targets for atherosclerosis, inflammation and hypertension 21.

The LBP is composed of residues belonging to four helices (H2, H4, H5, and H9) and a ß-strand 1 and 2 located between H5 and H6. It consists of a large nonspecific apolar cavity where many hydrophobic amino acid residues interact with the steroid nucleus through van der Waals contacts. The binding site is completed by a few polar residues that firmly tether the steroid molecule via hydrogen-bond networks formed with polar atoms found at both extremities of the ligand structures. The inherent nonspecificity of the hydrophobic interactions that loosely maintain the steroid in the steroid-binding cavity combined with the fact that the side chains of these residues are quite mobile and can adopt various conformations may explain how a steroid receptor of the NR family can bind several structurally different ligands.

The nuclear hormone receptors are a large family of transcription factors that directly bind and respond to ligands including steroids, thyroid hormone, retinoids, cholesterol by-products, lipids and haem1–4. These receptors contain poorly conserved A/B regions that in some cases act as potent transcriptional activators, provide sites of protein phosphorylation or form direct interactions with other receptor domains or regulatory proteins5. A central and highly conserved DBD contains two zinc-binding sites and the architectural elements capable of sequence-specific binding to DNA5,6. Hydrophobic molecules bind to the LBD, repositioning helix 12 into an active conformation that promotes the recruitment of co-regulators5,7. The nuclear receptor coactivators, including members of the steroid receptor coactivator (SRC) family, contain LXXLL motifs that dock to LBDs 8,9. There have been multiple structural studies of nuclear receptors involving either the LBD or DBD fragments alone6,7,10–12. However, there has been no successful visualization of any intact nuclear receptor. Consequently, there isinformation about how different domains interface to impart complex physiological and pharmacological properties. The peroxisome proliferator-activated receptors (PPARs) form heterodimers with the retinoid X receptor (RXR), and PPAR-γ. PPAR-γ and RXR-α form a non-symmetric complex, allowing the ligand-binding domain (LBD) of PPAR-γ to contact multiple domains in both proteins. Three interfaces link PPAR-γ and RXR-α, including some that are DNA dependent. The PPAR-γ LBD cooperates with both DNA-binding domains (DBDs) to enhance response-element binding. The A/B segments are highly dynamic, lacking folded substructures despite their gene-activation properties.

Steroid receptors bind as dimers to the cell created protein set for DNA response elements containing inverted base pair (bp) repeats of a hexameric half-site separated by 3 bp of spacer (IR3). Naturally occurring selective androgen response elements have recently been identified that resemble direct repeats of the hexameric half-site 1 bp (DR1). The 3D crystal structure of the androgen receptor (NR) DNA-binding domain bound to a selective NDR1 reveals an unexpected head-to-tail arrangement of the two protomers rather than the expected head-to-head arrangement seen in nuclear receptors bound to response elements of similar geometry.

The nuclear hormone receptors are a large family of transcription factors that directly bind and respond to ligands including steroids, thyroid hormone, retinoids, cholesterol by-products, lipids and haem. These receptors contain poorly conserved A/B regions that in some cases act as potent transcriptional activators, provide sites of protein phosphorylation or form direct interactions with other receptor domains or regulatory proteins. A central and highly conserved DBD contains two zinc-binding sites and the architectural elements capable of sequence-specific binding to DNA. Hydrophobic molecules bind to the LBD, repositioning helix H12 into an active conformation that promotes the recruitment of co-regulators. The nuclear receptor coactivators, including members of the steroid receptor coactivator (SRC) family, contain LXXLL motifs that dock to LBDs. There have been multiple structural studies of nuclear receptors involving either the LBD or DBD fragments alone .