# Steroid Hormone Receptor Dopaminergic and Ligand-Independent Activation

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## Abstract

Many studies have shown that there is significant cross-talk between signal transduction pathways and steroid receptors, in addition to the conventional hormone-dependent regulation of the activity of steroid/thyroid receptor family members. In some cases, modulation of kinase/phosphatase activity in cells leads to steroid receptor activation in the absence of hormone.The glucocorticoid receptor appears to be resistant to activation, so this novel mechanism may not be universal.without the presence of hormone Estrogen receptors, on the other hand, are Retinoic acid receptors, progesterone receptors, androgen receptors Retinoic acid receptors, retinoid X receptors, and vitamin D receptors are examples of such receptors.Under the right conditions, all of them exhibit ligand-independent activation.For many years, the prevailing view of how steroid hormone receptors exert their effects on gene transcription was that these intracellular receptor proteins undergo a transformation to a state capable of interacting with chromatin and regulating the transcription of specific genes upon association with their specific cognate ligands. In the field of biochemical endocrinology, it has become unspoken dogma that receptor activation is entirely dependent on this ligand-binding event.

Recent research by Bert O'Malley and colleagues, described here, has shown that a cell membrane receptor agonist, the neurotransmitter dopamine, can activate certain members of the steroid hormone receptor superfamily in a completely ligand-independent manner.

**Keywords:** Ligand-independent • Estrogen receptor

## Introduction

The ligand-inducible transcription factor superfamily comprises steroid hormone receptors, thyroid hormone receptors, retinoic acid receptors, and vitamin D3 receptors. The classical model of steroid hormone action, which has been known for over 15 years, includes hormone entering a cell by passive diffusion and binding to and inducing a conformational change in its associated receptor protein. It has long been assumed that these specific intracellular receptors are only activated when they bind to their cognate ligands [1].

Several members of the steroid receptor superfamily have previously been demonstrated to be activated by the neurotransmitter dopamine in the absence of the corresponding ligand. We investigated the potential of wild-type and mutant human oestrogen receptors to stimulate ER-dependent transcription of a transgene in a ligand-independent manner. Dopamine was nearly as effective as 17 beta-estradiol in inducing chloramphenicol acetyltransferase activity of the reporter gene in cells expressing the wild-type ER in a dose-dependent manner; simultaneous addition of suboptimal concentrations of 17 beta-estradiol and dopamine stimulated transcription more than either compound alone [2].

Dopamine alone was unable to induce gene expression in cells expressing [Val400]ER mutant receptors, but treatment with 17 beta-estradiol produced a synergistic increase in transcription, implying that the ligand may change the mutant receptor's conformation, allowing it to be activated later by a dopaminergic signalling mechanism. Dopamine-stimulated gene expression in cells expressing either form of ER was undetectable in the presence of the antiestrogen. However, treating cells expressing wild-type ER with trans-4-hydroxytamoxifen and dopamine at the same time resulted in transgene expression that was additive in nature when compared to either compound alone; similarly, treating cells expressing ER with both compounds at the same time resulted in a synergistic increase.

Our findings suggest that ligand-dependent and ligand-independent ER activation follow distinct pathways, with the latter occurring in a variety of target tissues modulated by receptor ligands.

The cell type, promoter, and activator of a steroid receptor determine whether it responds to a signal by inducing transcription of a target gene in the absence of hormone. The mechanism(s) that induce ligand-independent activation are currently of great interest.

Because the signals that activate receptors cause protein phosphorylation, altered phosphorylation of receptors and/or proteins that associate with the receptors are likely to be important in ligand-independent activation. There is strong evidence that altered receptor phosphorylation contributes to ligand-independent activation of the oestrogen receptor. Proteins in heat shock protein complexes, corepressors, and/or steroid receptor coactivators are also possible targets.

All of the major receptor proteins in this superfamily's cDNAs have been cloned and sequenced over the last five to six years.' The N-terminal region of the receptors is highly variable and shows little homology among the receptor proteins. The mineralocorticoid receptor's domain is 603 amino acids long, while the vitamin D receptor's domain is 25 amino acids long [3].

This hypervariable region is usually where the epitopes of antibodies raised against receptors are found.Many proteins have been labelled orphan receptors because their ligands and/or functions have yet to be identified. All members of the family have carboxyl terminal ligand-binding domains, which are also important for receptor dimerization (for a review of steroid receptor structure, see). All members of the family share DNA-binding domains with two Zn finger motifs located at the amino terminal of the hormone-binding domain. The amino termini of receptors vary greatly in length and sequence; this region is important for transcriptional activation and/or repression.

A further comparison of the deduced amino acid sequences for these receptors reveals three major internal regions (I-III) of amino acid conservation common to all members of this family. Region I is a highly conserved 66 amino acid sequence that constitutes the DNA-binding domain. This region contains nine cysteine residues, eight of which are believed to form two zinc fingers with each finger containing one zinc atom. The DNA-binding domain of the receptor contains the sequences that recognize the specific steroid response elements that are located in the flanking regions of target genes [4].

A closer look at the deduced amino acid sequences for these receptors reveals three major internal regions (I-III) of amino acid conservation that are shared by all members of this family. The DNA-binding domain is comprised of Region I, a 66 amino acid sequence that is highly conserved. This region contains nine cysteine residues, eight of which are thought to form two zinc fingers, each with one zinc atom. The receptor's DNA-binding domain contains sequences that recognise specific steroid response elements found in the flanking regions of target genes.

In the absence of hormones, the receptors may be divided into two types depending on their interactions with other proteins. Depicts the traditional ligand-dependent activation of heat shock protein-interacting steroid/thyroid hormone receptor family members. This category includes

oestrogen, progesterone, androgen, glucocorticoid, and mineralocorticoid receptors. In the absence of hormones, each receptor monomer is linked to a protein complex that includes hsp90 and several other proteins.

This receptor complex is cytoplasmic or loosely attached in the nucleus and is incapable of binding to DNA. The steroid enters the cell and binds to the receptor's ligand binding domain, causing a conformational shift that promotes dissociation of the protein complex and tight binding to DNA. The receptors bind as homodimers to particular steroid response elements, which are inverted palindromes separated by three nucleotides, and then interact with basal transcription factors, coactivators, and other transcription factors to stimulate and/or inhibit transcription of the target gene. addition of suboptimal concentrations of 17 beta-estradiol and dopamine [5].

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