NRN Nuclear Receptor News

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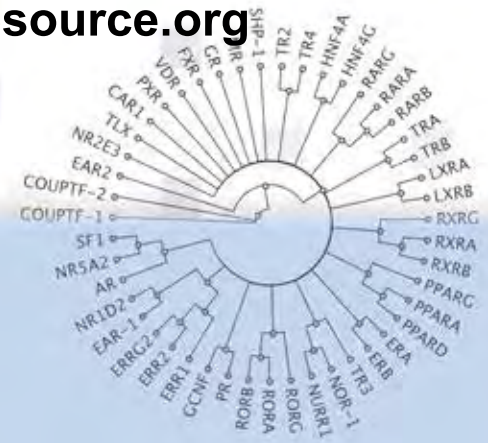

In This Edition

NRN Nuclear Receptor News

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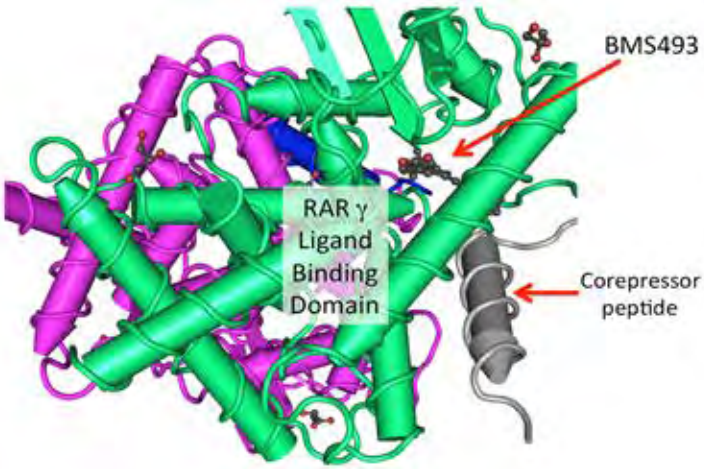
Welcome to the Antagonist and Inverse Agonist Issue

Ligand or drug-receptor interactions are not the same as the "lock-and-key" model that is often used to typify an association between a chemical and a cognate protein. In fact, the ultimate effect of a ligand-receptor complex can manifest in a continuum of responses ranging from pure agonist (occupation with full efficacy) to pure antagonist (occupation with no efficacy) with partial agonism/antagonism in between. In recent years other types of ligands have emerged including "Selective Receptor Modulators (SRMs)" and "Inverse Agonists", both of which are dependent on the conformation of the liganded-receptor complex and resultant protein-protein interactions. In this issue of Nuclear Receptor News we will outline the differences between three types of ligands that may result in similar dose-response curves, namely antagonist, inverse agonists or overtly toxic compounds.



For more information, please visit the Nuclear Receptor Resource at http://nrresource.org

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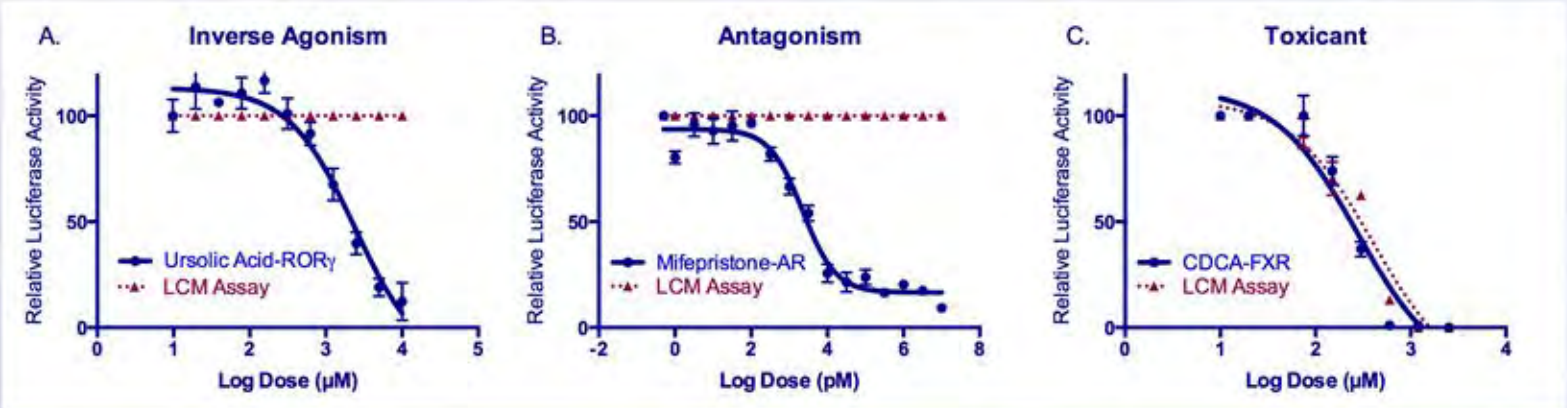
Antagonists & Inverse Agonists

Distinguishing an Antagonist, Inverse Agonist or Toxicant

When discussing a drug that binds with specificity to a receptor, in other words a ligand, there are several classifications that are dependent on the biological response. An agonist is a ligand that increases the activity of a receptor above its basal, or constitutive level. An inverse agonist is an agent that binds to the same receptor as an agonist but induces a pharmacological response opposite to that of an agonist. A prerequisite for an inverse agonist response is that the receptor must have high constitutive or basal activity in the absence of an identifiable ligand. There are several examples of inverse agonists of nuclear receptors, in particular of the estrogen receptor-related receptors (ERRα, β, γ) (1), retinoic acid-related orphan receptors (RORα, β, γ), (2)), peroxisome proliferator-activated receptor δ (PPARδ (3)) and constitutive androstane receptor (CAR-1) (4). As shown in Panel A, ursolic acid is an inverse agonist of RORγ leading to a decrease in activity following a typical sigmoidally shaped dose-response curve. A receptor antagonist is a type of ligand that blocks or ameliorates agonist-mediated responses. Androgen receptor antagonists are examined in reporter assays by providing a constant amount of agonist (i.e. testosterone), then supplying the potential antagonist; shown in Panel B is ability of mifepristone to decrease agonist-induced AR activity. When performing a cell-based assay, such as a reporter gene assay for a given receptor, an overtly toxic compound will lead to a dose-dependent decrease in the response being measured, as shown in Panel C with the bile acid CDCA in an farnesoid X receptor (FXR) reporter assay. This decrease in reporter gene activity may be the result of decreased cell numbers or decreased activity of the transcription and translational capability of surviving cells. The simplest way to distinguish between these three very similar dose response curves, is to perform a cell viability assay. Shown in the figure below are the results of a convenient cell viability assay that can be performed sequentially with the reporter assay called Live Cell Multiplex Assay (LCMA, INDIGO Biosciences, Inc.) although other platforms may be employed. An inverse agonist will cause a decrease in reporter activity without affecting the cell viability (Panel A) whereas an overtly toxic compound (Panel C) will have a dose-response for reporter gene read-out that is very similar to that of viability. The difference between an inverse agonist and an antagonist is slightly harder to address, but both should not cause toxicity within the dose range examined. A pure antagonist will have affinity but no efficacy for their cognate receptors, and binding will disrupt the interaction and inhibit the function of an agonist or inverse agonist at receptors. Thus, by itself there should be little or no activity, but in the presence of an agonist, there should be a decreased activity; an inverse agonist will decrease reporter gene activity without the need to stimulate with an agonist.



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To learn more about inverse agonists, antagonists and basic terms in receptor biology, please visit the nuclear receptor resource (http://nrresoure.org)

New INDIGO RARα, RARβ, and RXRβ Assay Kits Simplify Retinoic Acid Receptor Research

INDIGO Biosciences, The Nuclear Receptor Experts, announce three new products to its growing line of INDIGO Nuclear Receptor Assay Kits. The INDIGO RARα, RARβ, and RXRβ Assay Kits are robust, easy-to-use, high and low throughput screening solutions for researchers in drug discovery and development research and toxicology studies.

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