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BIOGRAPHY

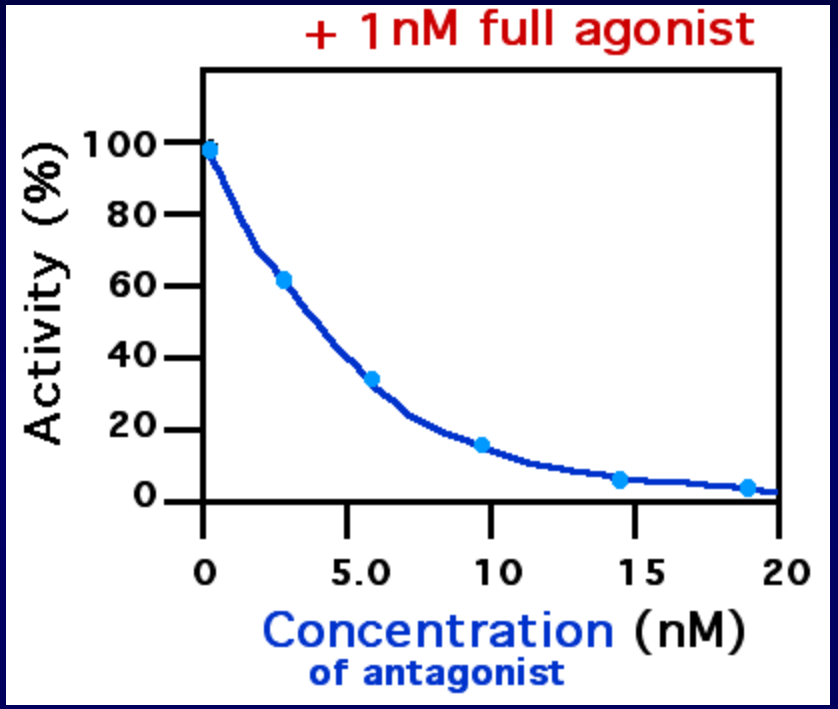
HUGO R ARIAS ASSOCIATE PROFESSOR DEPARTMENT OF PHARMACEUTICAL SCIENCES COLLEGE OF PHARMACY MIDWESTERN UNIVERSITY GLENDALE AZ 85308 USA ASSISTANT PROFESSOR OF PHARMACEUTICAL SCIENCES DEPARTMENT OF PHARMACEUTICAL SCIENCES COLLEGE OF PHARMACY WESTERN UNIVERSITY OF HEALTH SCIENCES POMONA CA USA RESEARCH ASSISTANT PROFESSOR DEPARTMENT OF PHARMACOLOGY AND THERAPEUTICS COLLEGE OF MEDICINE UNIVERSITY OF FLORIDA GAINESVILLE FL USA ADJUNCT INVESTIGATOR NATIONAL COUNCIL OF SCIENTIFIC AND TECHNOLOGICAL RESEARCH CONICET ARGENTINA ASSISTANT INVESTIGATOR NATIONAL COUNCIL OF SCIENTIFIC AND TECHNOLOGICAL RESEARCH CONICET ARGENTINA PROFESSIONAL ASSISTANT NATIONAL COUNCIL OF SCIENTIFIC AND TECHNOLOGICAL RESEARCH CONICET ARGENTINA. HE HAS RECEIVED A PHD IN BIOCHEMISTRY FROM THE NATIONAL SOUTHERN UNIVERSITY BAHÍA BLANCA ARGENTINA IN 1990. HE HAS RECEIVED A MASTER OF SCIENCE IN BIOCHEMISTRY FROM THE NATIONAL SOUTHERN UNIVERSITY BAHIA BLANCA ARGENTINA IN 1982. HE HAS COMPLETED HIS BA OF SCIENCE IN BIOCHEMISTRY IN THE NATIONAL SOUTHERN UNIVERSITY BAHÍA BLANCA ARGENTINA IN 1982. HE HAS COMPLETED HIS DIPLOMA OF CHEMIST IN THE NATIONAL SOUTHERN UNIVERSITY BAHÍA BLANCA ARGENTINA IN 1980.

RESEARCH INTEREST

CYS-LOOP LIGAND-GATED ION CHANNELS- NICOTINIC ACETYLCHOLINE RECEPTORS - AGONISTS, COMPETITIVE ANTAGONISTS, NONCOMPETITIVE ANTAGONISTS, POSITIVE AND NEGATIVE ALLOSTERIC MODULATORS THERMODYNAMICS OF LIGAND-RECEPTOR INTERACTIONS, DRUG ADDICTION DEPRESSION AND ANTIDEPRESSANTS ALZHEIMER'S DISEASE. MODULATION OF ANGIOGENESIS BY NICOTINIC RECEPTORS.

Antagonists, Overview

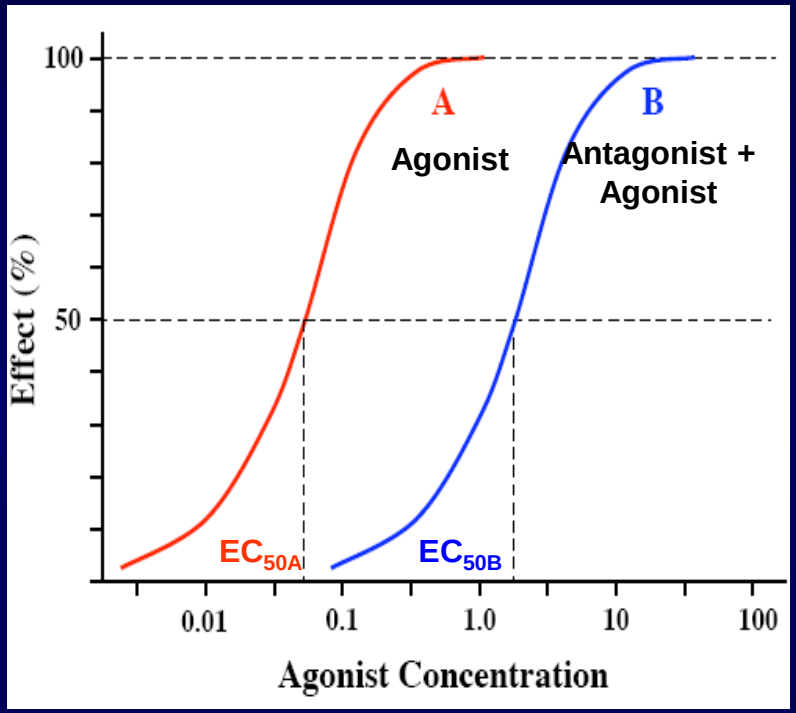
- **Definition**
  "An antagonist is a substance that does not provoke a biological response itself, but blocks or reduces agonist-mediated responses"



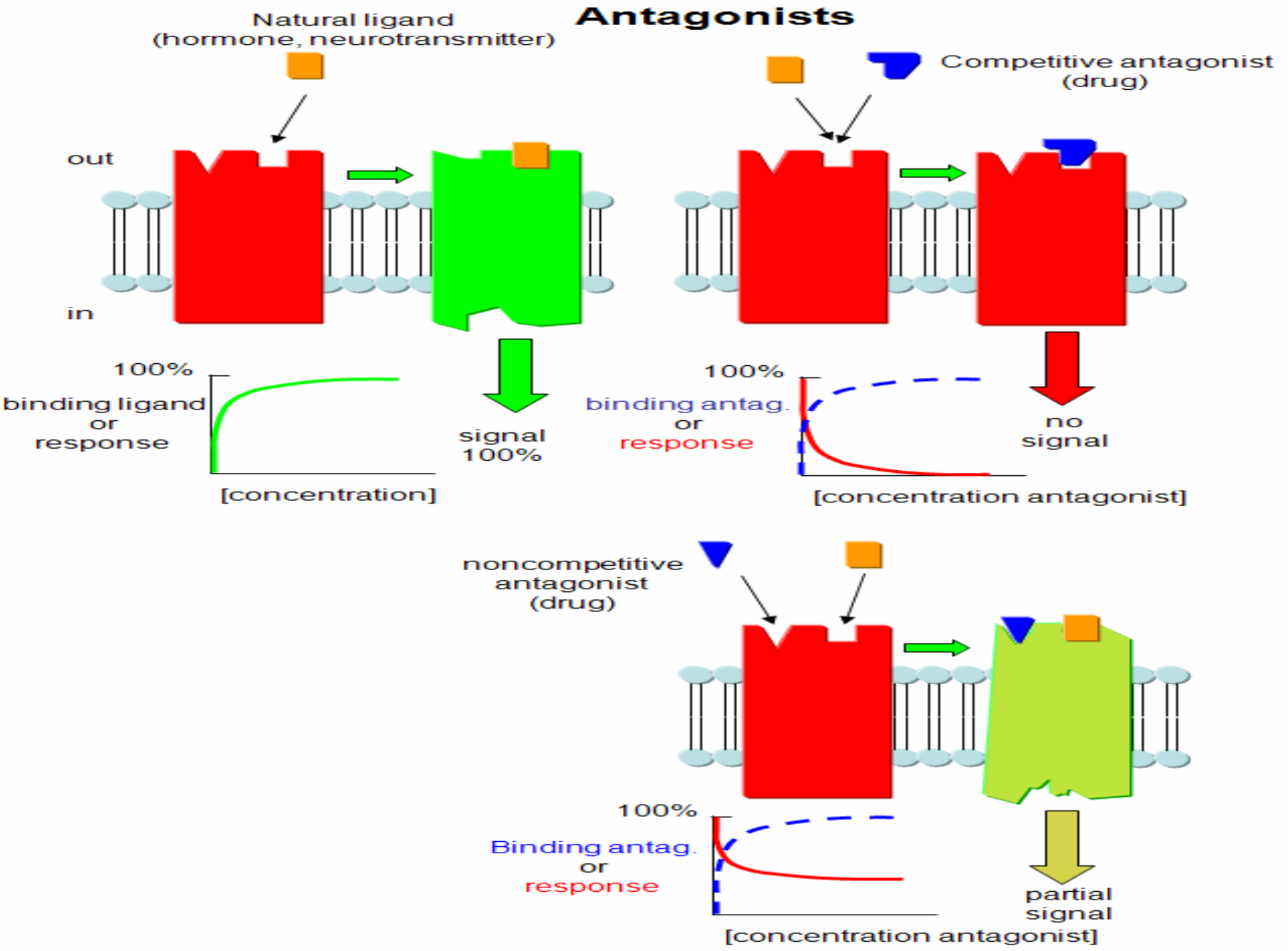
- Antagonists have affinity but no efficacy for their cognate receptors
- Binding of antagonist to a receptor will inhibit the function of a partial agonist, an agonist or inverse agonist at that receptor
- Antagonists mediate their effects by binding to the active site or to allosteric sites on receptors or they may interact at unique binding sites not normally involved in the biological regulation of the receptor's activity.
- Antagonist activity may be reversible or irreversible depending on the longevity of the antagonist–receptor complex which in turn depends on the nature of antagonist receptor binding.

Antagonists, 1-Competitive reversible antagonist

- **It binds to same site on receptor as agonist**
- inhibition **can be** overcome by increasing agonist concentration **(i.e., inhibition is reversible)**
- No significant depression in maximal response **(E_{max} ??)**
- The agonist dose-response curve will be shifted to the right (without a change in the slope of the curve)
- Maximal response occurs at a higher agonist concentration than in the absence of the antagonist
- **It primarily affects agonist potency**
- Clinically useful
- Example: Prazosin at α adrenergic receptors

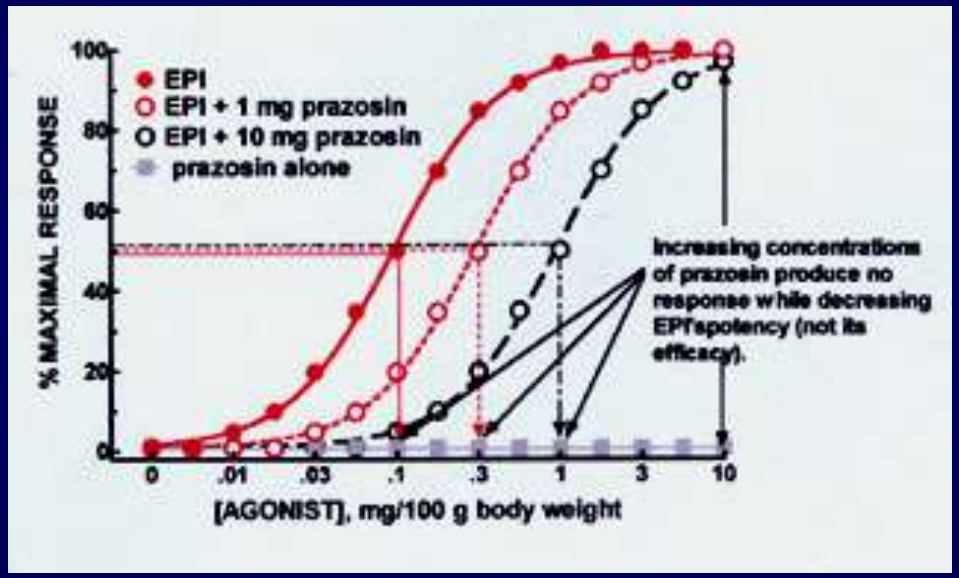


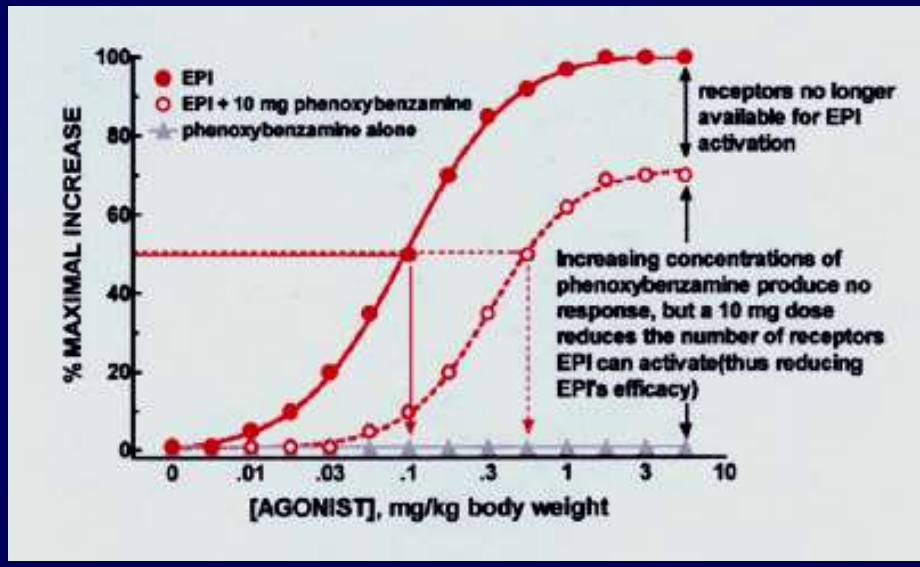
Antagonists



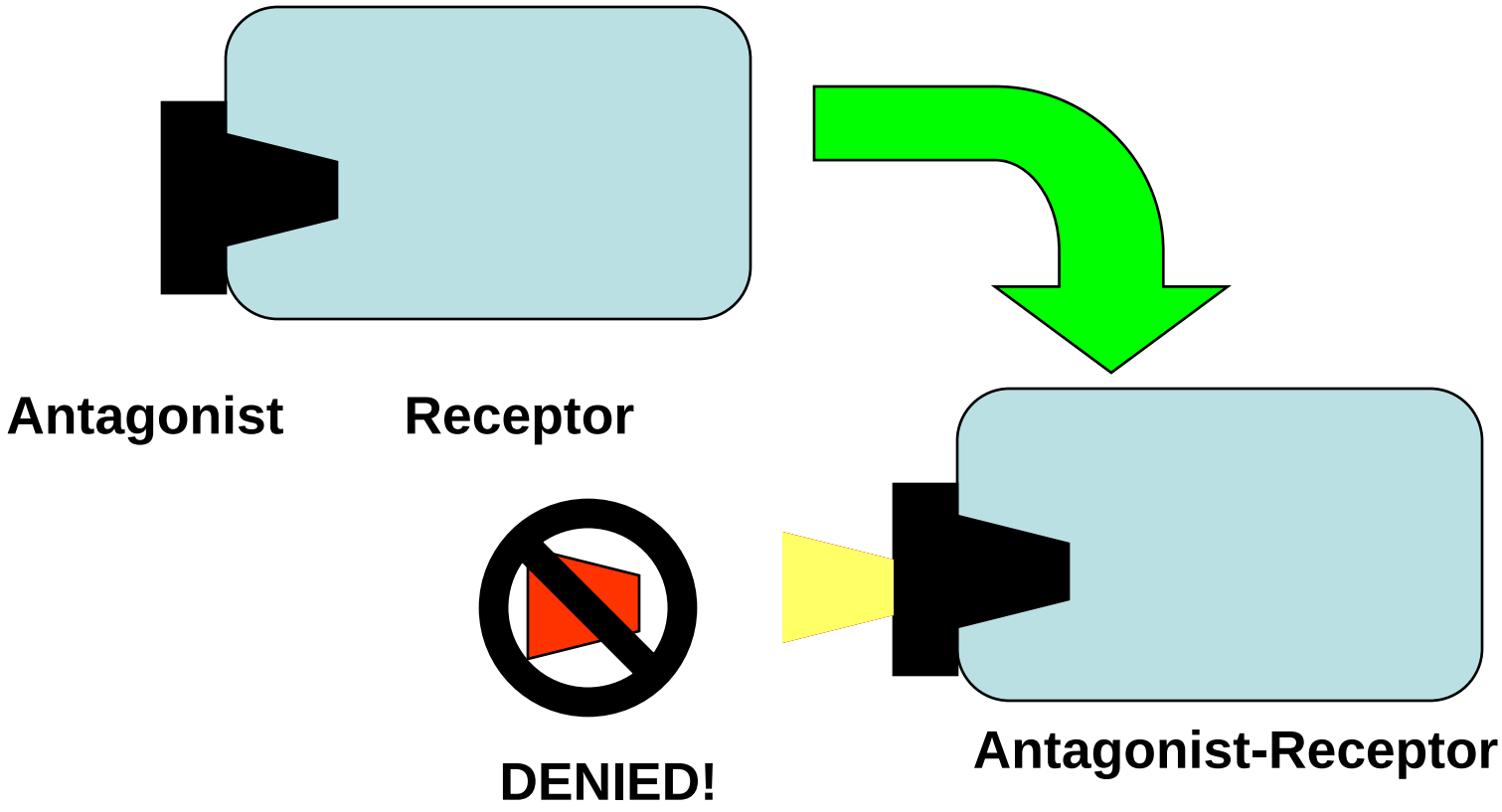
Antagonists, contd.

Competitive reversible antagonist vs **Competitive irreversible antagonist**



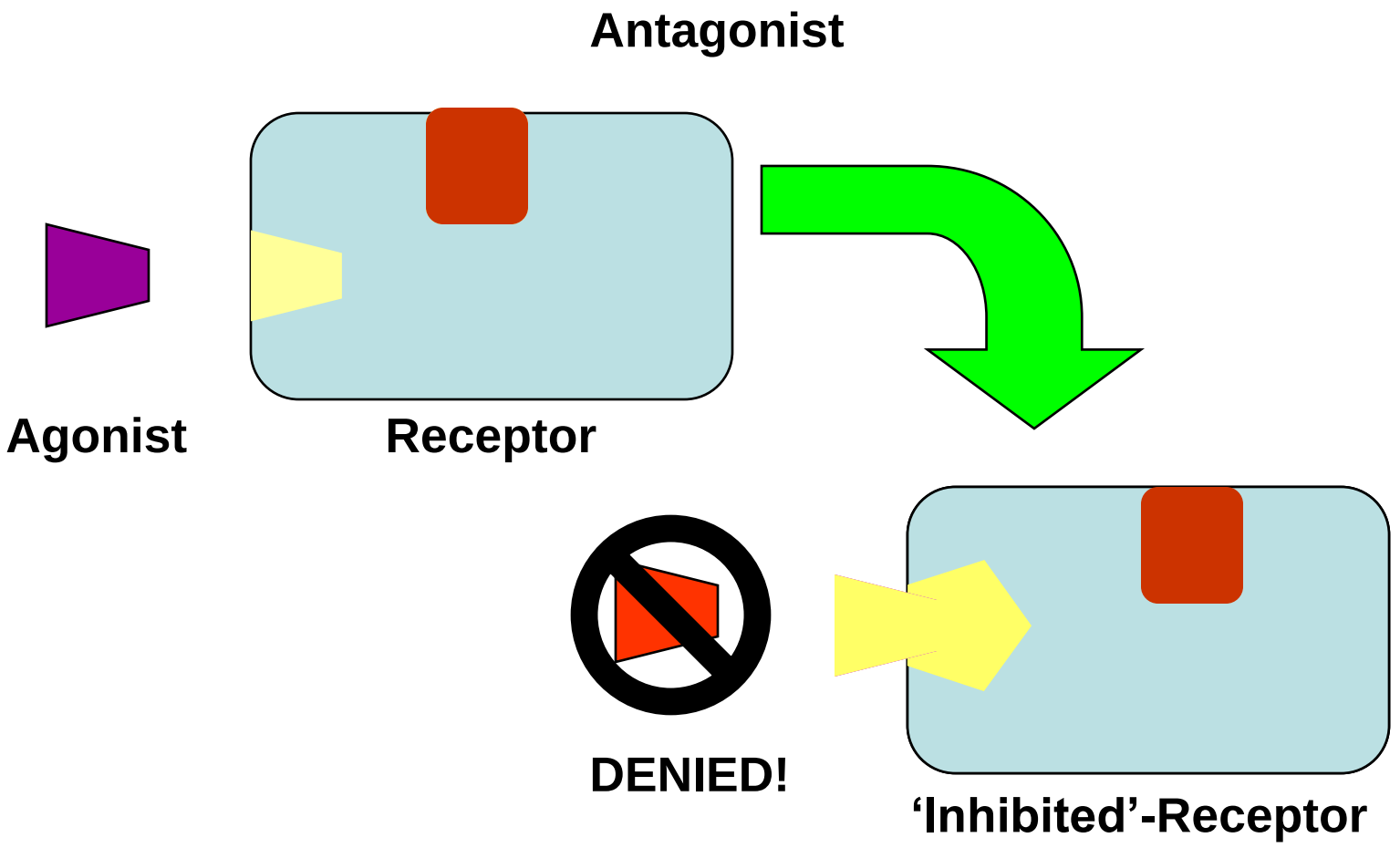


Competitive Antagonists, In Motion



Receptors.exe

Non-competitive Antagonist, In Motion

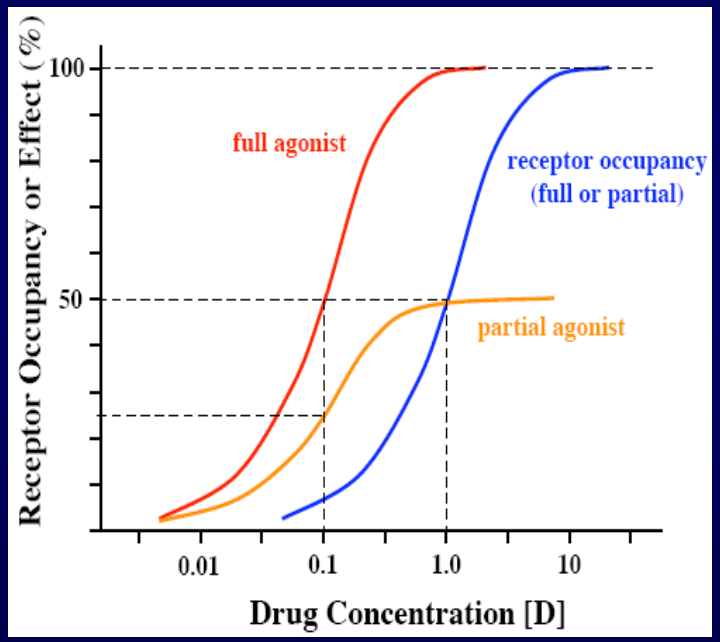


Drug Receptor Interactions, Full vs Partial Agonist

- **Full agonist**
  "Drug with high efficacy enough to elicit a maximal tissue response"

- **Partial agonist**
  "Drug with intermediate level of efficacy, such that even when 100% of the receptors are occupied, the tissue response is submaximal"

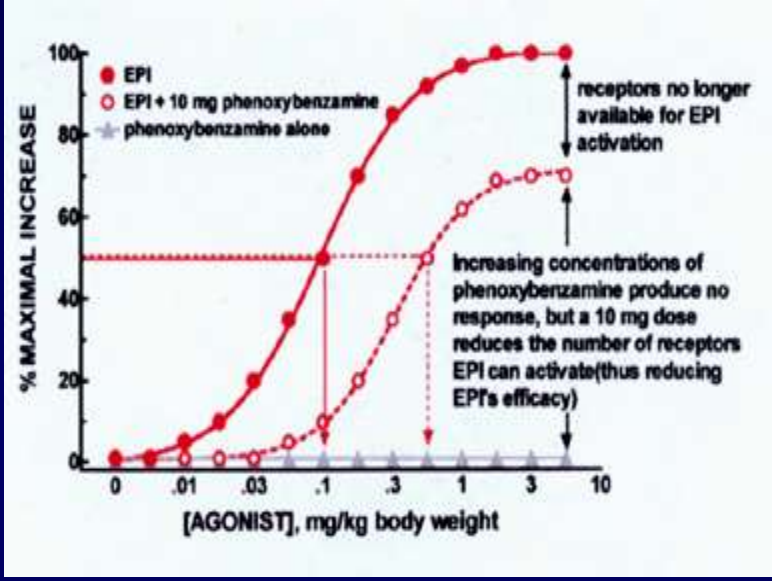
  - exhibits similar potency (EC_{50}), but lower efficacy (E_{max})
  - produces concentration-effect curves that resemble those observed with full agonists in the presence of an irreversible antagonist
  - compared to full agonist both can exhibit identical receptor affinity (the blue curve)
  - **the failure of partial agonists to produce a maximal response is not due to decreased receptor affinity → partial agonists competitively inhibit the responses produced by full agonists**
  - many clinical agents used as antagonists are actually partial agonists



  - For example, pindolol, **a β-adrenoceptor "partial agonist,"** may act as either an agonist (if no full agonist is present) or as an antagonist (if a full agonist such as isoproterenol is present). Propranolol is devoid of agonist activity, i.e., it is a **pure antagonist**

Antagonists, 2- Competitive irreversible antagonist

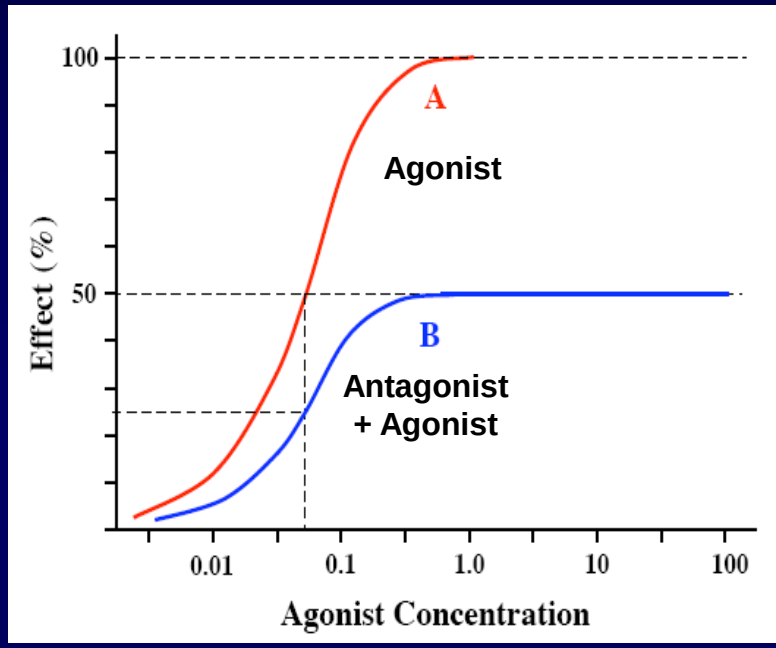
- **It binds to same site on receptor as agonist**
- **The antagonist possesses reactive group which forms covalent bond with the receptor → the antagonist dissociates very slowly, or not at all**
- inhibition **cannot** be overcome by increasing agonist concentration **(i.e., inhibition is irreversible)**
- **Maximal response is depressed (i.e., E_{max} is decreased)**
- The agonist dose-response curve will be shifted to the right (the slope of the curve will be reduced)
- Agonist potency may or may not be affected



- The only mechanism the body has for overcoming the block is to **synthesize new receptors**
- Experimental tools for investigating receptor functions
- Example: phenoxybenzamine at α adrenergic receptors

Antagonists, 3- Non-competitive antagonist

- **It does not bind to the same receptor sites as the agonist**. It would either:
  - bind to a distinctly separate binding site from the agonist →decreased affinity of the receptor for the agonist, “allosteric inhibition”,
  - prevent conformational changes in the receptor required for receptor activation after the agonist binds → “allosteric inhibition”,
  - or alternatively block at some point the chain of events that leads to the production of a response by the agonist
- Inhibition **cannot** be overcome by increasing agonist concentration **(irreversible)**
- **Agonist maximal response will be depressed**
- Agonist dose-response curve will be shifted to the right (the slope of the curve will be reduced)
- Agonist potency may or may not be affected



- Example: the noncompetitive antagonist action of crystal violet (CrV) on nicotinic acetylcholine receptors is explained by an allosteric mechanism in which the binding of CrV to the extracellular mouth of the resting receptor leads to an inhibition of channel opening

Antagonists, contd.

4. **Physiologic (functional) antagonist**
   Physiologic antagonism occurs when the actions of two agonists working at two different receptor types have opposing (antagonizing) actions

   Example 1: Histamine acts at H_1 receptors on bronchial smooth muscle to cause bronchoconstriction, whereas adrenaline is an agonist at the β_2 receptors bronchial smooth muscle, which causes bronchodilation.
   Example 2: histamine acts on receptors of the parietal cells of the gastric mucosa to stimulate acid secretion, while omeprazole blocks this effect by inhibiting the proton pump

5. **Chemical antagonist**
   Chemical antagonism occurs when two substances combine in solution → the active drug is lost

   Example : Chelating agents (e.g., dimercaprol) that bind heavy metals, and thus reduce their toxicity

6. **Pharmacokinetic antagonist**
   Pharmacokinetic antagonist effectively reduces the concentration of the active drug at its site of action
   Example: phenobarbital accelerates the rate of metabolic degradation of warfarin

SIGNATURE

Hugo R. Arias

Journals

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