Pharmacodynamics

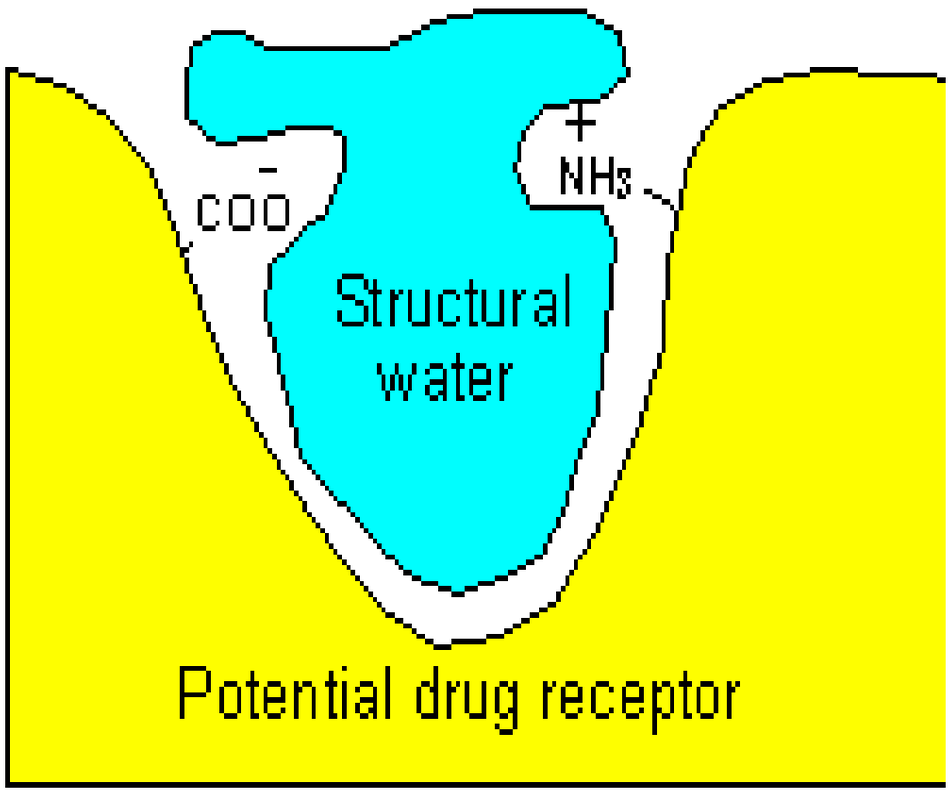
Lecture 5

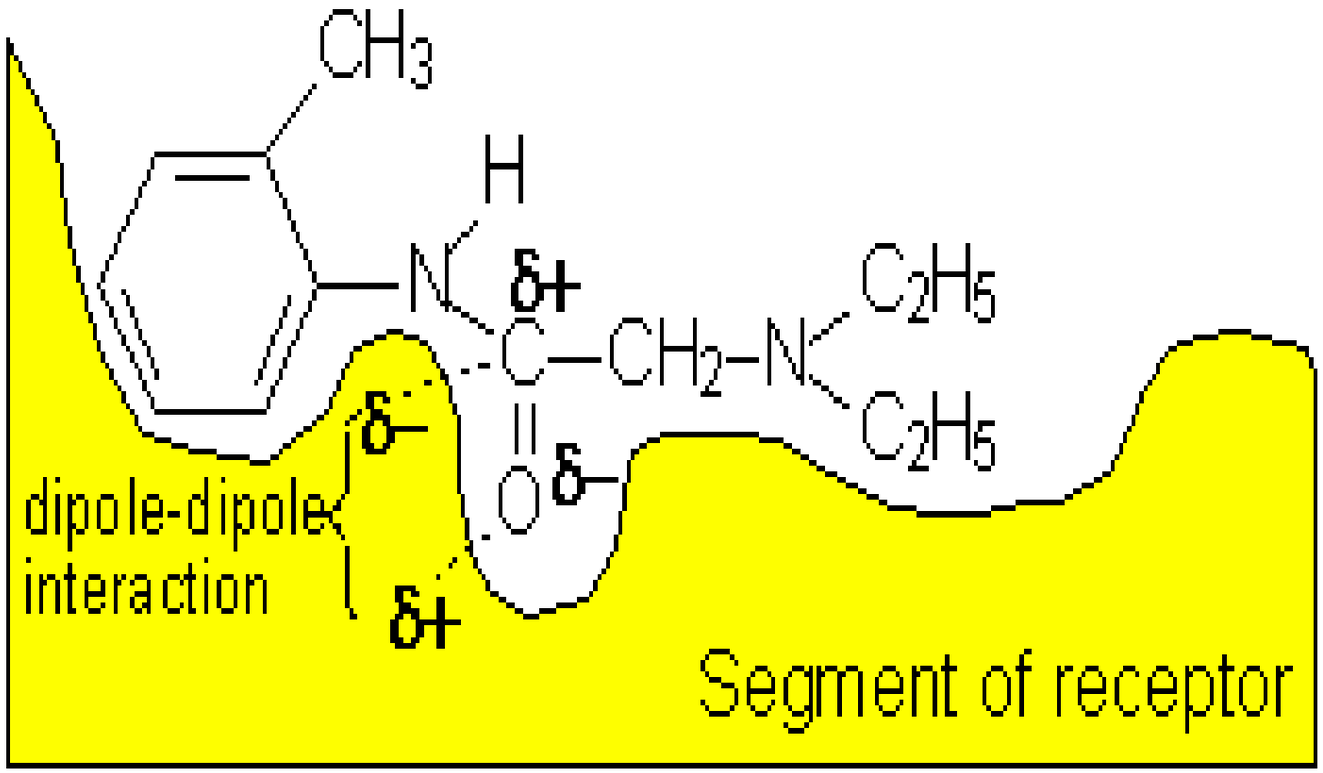
19 Sept 2018

Receptors are an Excellent Drug Target

- Activated receptors directly, or indirectly, regulate cellular biochemical processes within and between cells to change cell function.
- Recognition sites are precise molecular regions of receptor macromolecules to which the ligand binds providing:
- Specificity: Only a subset of receptors will be targets
- Selectivity: Since receptors are coupled to specific signaling pathways
- Sensitivity: Receptor binding events are amplified intracellularly

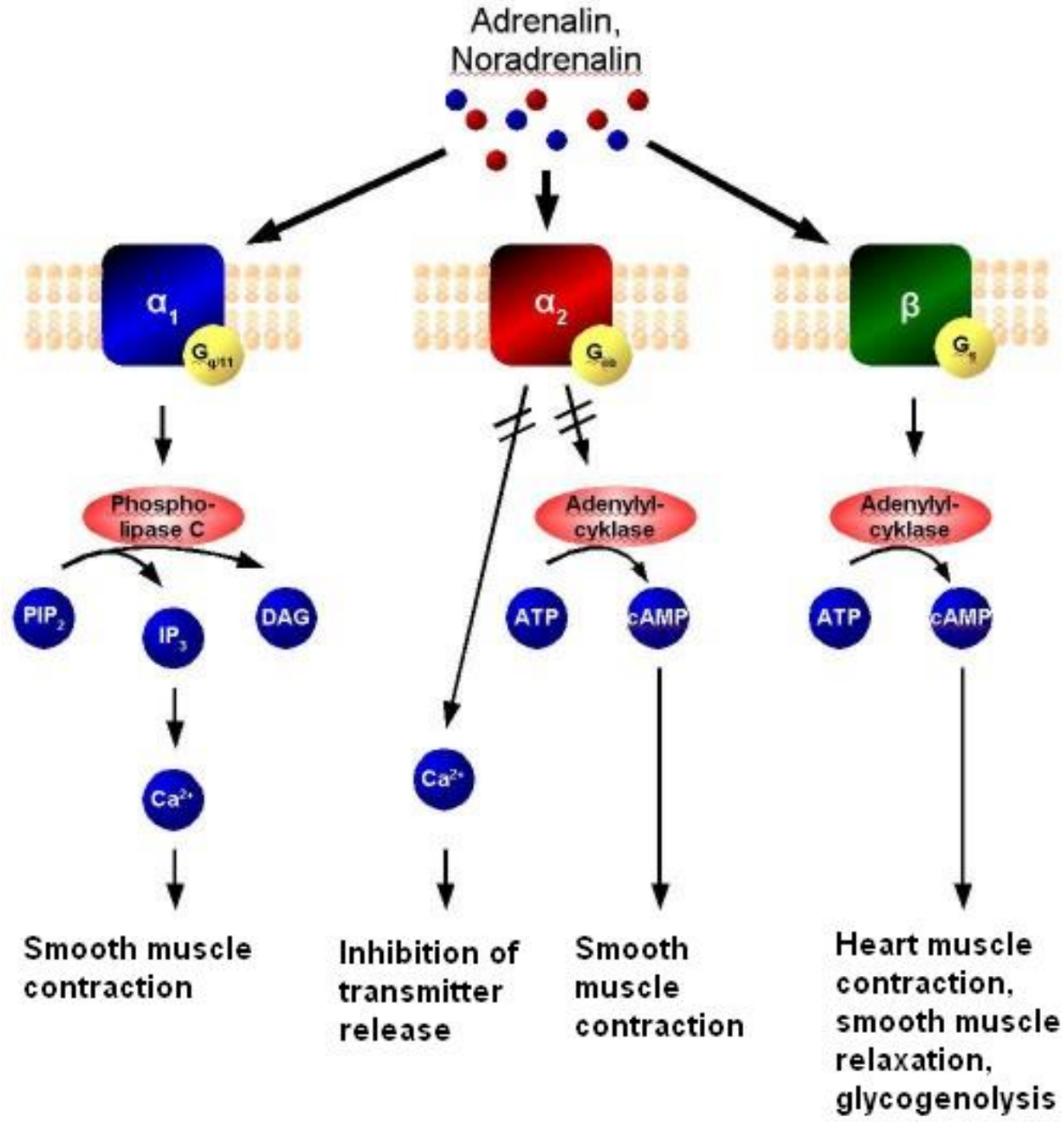
Specificity:**Lock and key**





The precise fit required of the ligand ……”**KEY**
The activation of the receptors…….The opening of the “**LOCK**”

This interaction shows high degree of **specificity**


Adrenalin,
Noradrenalin
α1
Gq/11
α2
Gio
β
Gs
Phospho-
lipase C
Adenylyl-
cyklase
Adenylyl-
cyklase
PIP2
IP3
DAG
Ca2+
ATP
cAMP
ATP
cAMP
Ca2+
Smooth muscle
contraction
Inhibition of
transmitter
release
Smooth
muscle
contraction
Heart muscle
contraction,
smooth muscle
relaxation,
glycogenolysis

(a) Signaling pathway	(b) Number of molecules activated
RECEPTION Binding of epinephrine to G protein-linked receptor	1 molecule
TRANSDUCTION Inactive G protein → Active G protein	10^2 molecules
Inactive adenylyl cyclase → Active adenylyl cyclase	10^2 molecules
ATP → Cyclic AMP	10^4 molecules
Inactive protein kinase A → Active protein kinase A	10^4 molecules
Inactive phosphorylase kinase → Active phosphorylase kinase	10^5 molecules
Inactive glycogen phosphorylase → Active glycogen phosphorylase	10^6 molecules
RESPONSE Glycogen → Glucose-1-phosphate	10^8 molecules

Signal Amplification

- Receptor binding are amplification terms of duration and intensity

- Example: G-protein coupled receptors

- Phenomena that account for the amplification:

1. The receptor drug-complex can interact with many G proteins thereby multiplying the organ signal many folds.

2. The activated G-protein persists for longer duration than the original receptor-drug complex

So what are the consequences of this amplification????

Spare receptors

Only a fraction of total receptors for a specific ligand may need to be occupied to elicit a maximum response.

Examples:

- Insulin receptors are estimated to have 99% of the receptors as spare receptors…….. large functional reserve to ensure adequate control of glucose uptake.

- Only 5-10% of beta adrenoceptors are space……..little functional reserve exist in the failing heart. So most receptors need to be occupied for a maximum effect

Two-state model of drug-receptor interaction

- The receptor is postulated to exist in the inactive, nonfunctional form (Ri) and in the activated form (Ra).
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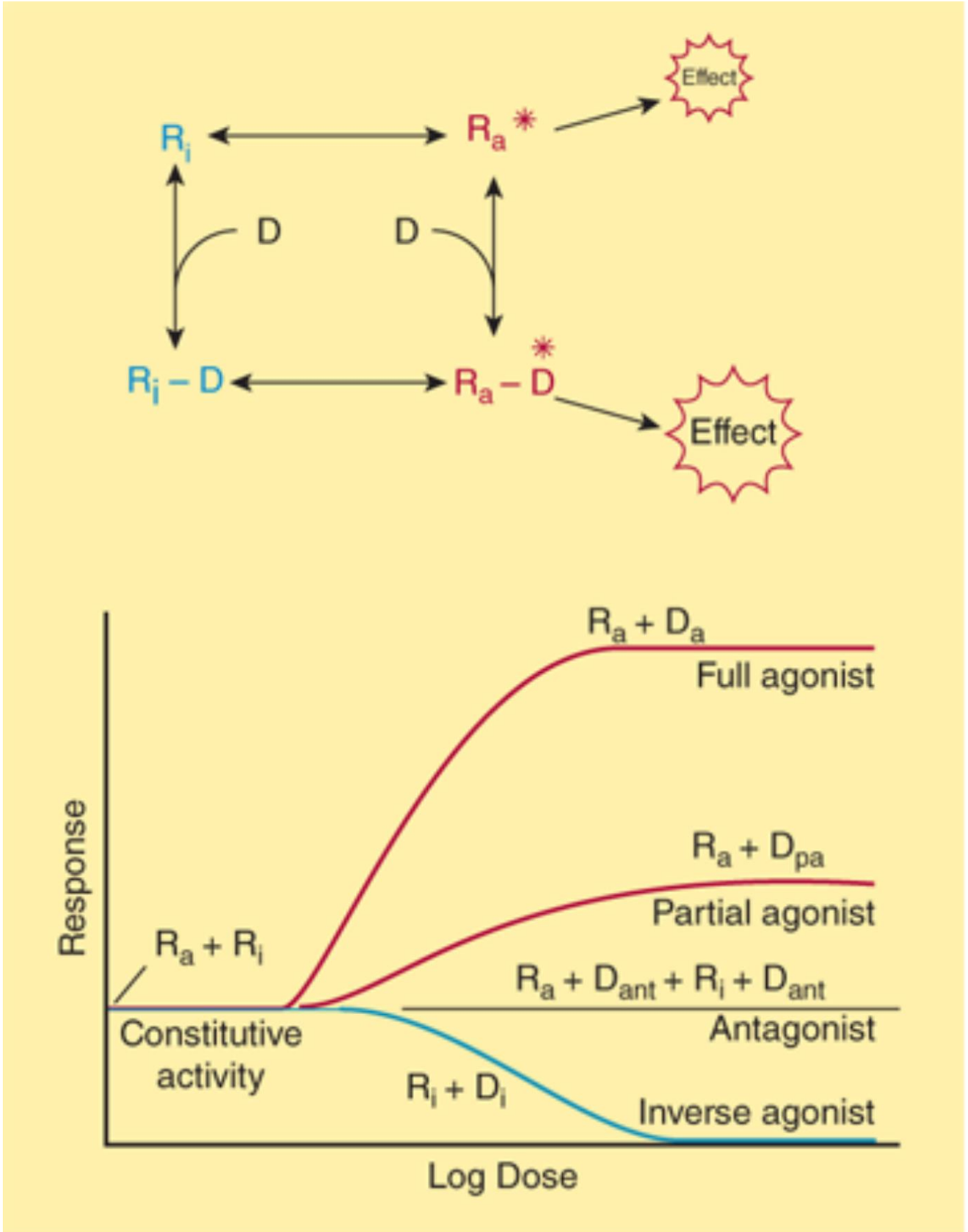
- Thermodynamic considerations indicate that even in the absence of any agonist, some of the receptor pool must exist in the Ra form some of the time and may produce the same physiologic effect as agonist-induced activity.
- Agonists have a much higher affinity for the Ra configuration and stabilize it, so that a large percentage of the total pool resides in the Ra–D fraction and a large effect is produced

Constitutive Activity

- The effect of receptors, occurring in the absence of agonist, is termed constitutive activity.
- The recognition of constitutive activity may depend on the receptor density, the concentration of coupling molecules (if a coupled system), and the number of effectors in the system.



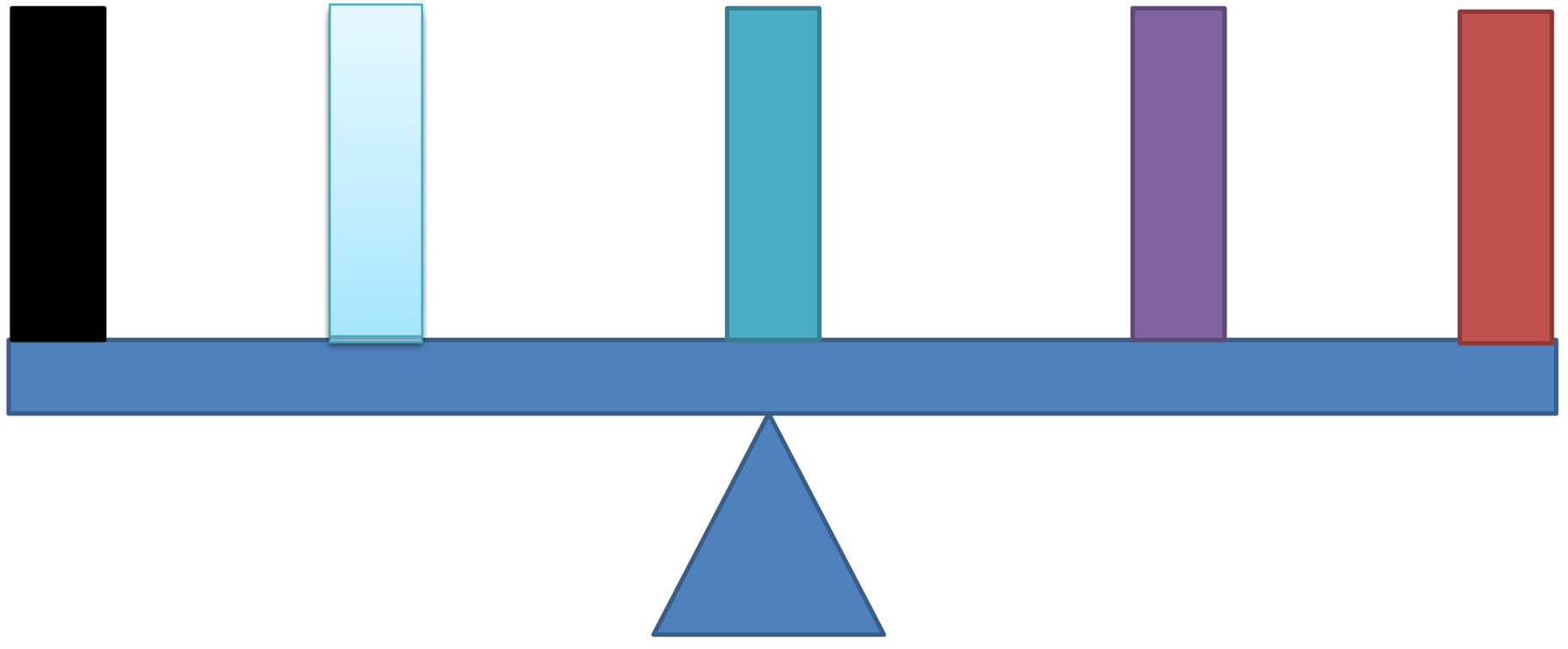
Source: Bertram G. Katzung, Anthony J. Trevor: Basic & Clinical Pharmacology, 13th Ed.
www.accesspharmacy.com

Inverse agonists:

While antagonists are traditionally thought to have no functiona

Competitive & Irreversible Antagonists

- Receptor antagonists bind to receptors but do not activate th
- The primary action of antagonists is to reduce the effects of a
- Inverse agonists shift equilibrium towards the inactive conformat
- Effect obvious *if* much constitutive activity



Full agonist

Partial agonist

Antagonist

Partial inverse agonist

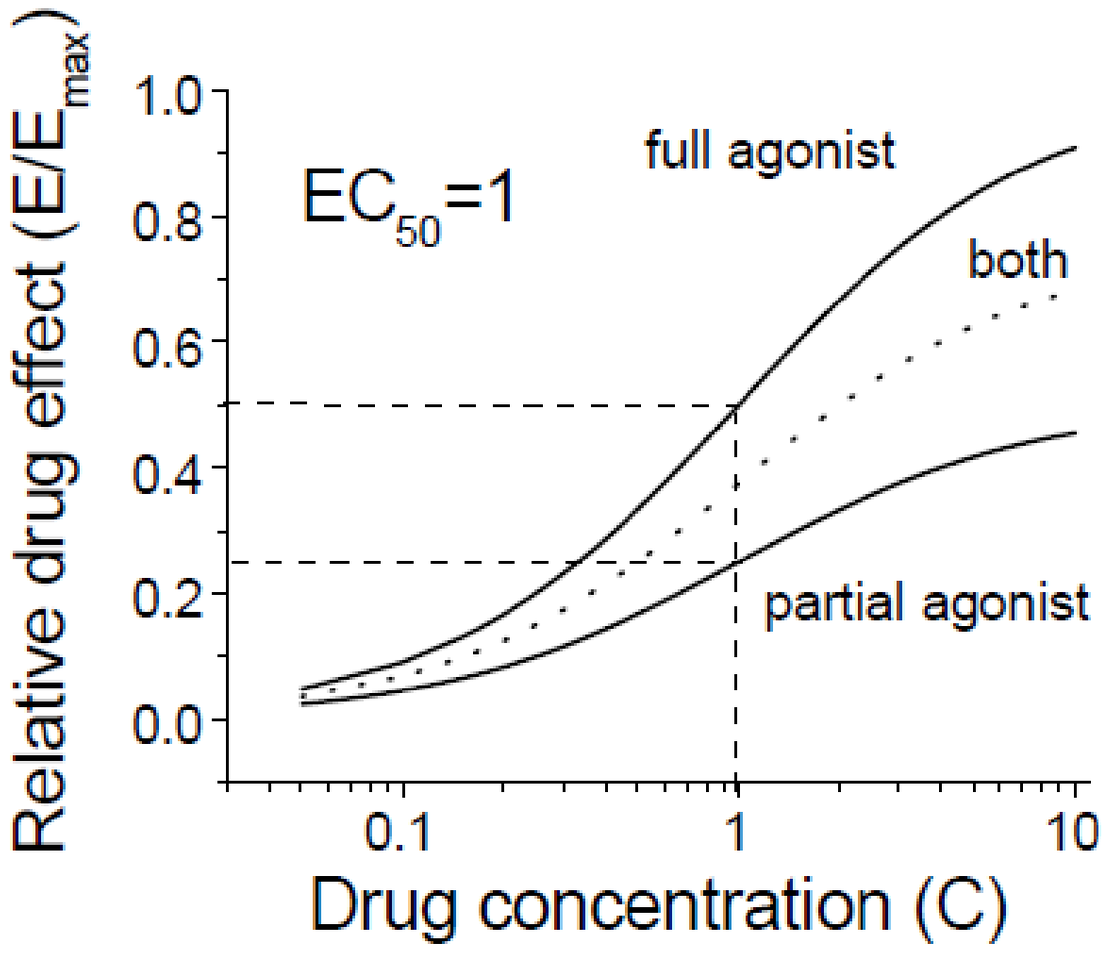
Full inverse agonist

Inverse agonists

- Inverse agonists shift equilibrium towards the inactive conformation
- Effect obvious *if* much constitutive activity

Two-state model of drug-receptor interaction

- Full agonists shift equilibrium “fully” towards the active conformation
- Partial agonists shift equilibrium “partially” towards the active conformation
- Sub-maximal effect with receptors completely occupied


Relative drug effect (E/E$_{max}$)
1.0
0.8
0.6
0.4
0.2
0.0
EC$_{50}$=1
full agonist
both
partial agonist
0.1
1
10
Drug concentration (C)