Mechanisms of drug action; non-specific, specific.

*

Receptors and ligand binding.

*

Receptor subtypes; neuronal autoreceptors, heteroreceptors

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CEITEC (Central European Institute of Technology) Masaryk University

Mechanisms of drug effects

SPECIFIC - RECEPTOR MEDIATED

DRUG ⟷ RECEPTOR

drug = ligand of the receptor

afinity
&
intrinsic activity = efficacy

- direct
- indirect

NONSPECIFIC – non-receptor

- physical
  (e.g. osmotic diuretics)
- chemical
  (e.g. antacids)

- impact on function
  of the receptor system
  functioning
  (beyond the receptor)

Mechanisms of drug effects

SPECIFIC - RECEPTOR MEDIATED

DRUG ⟺ RECEPTOR

affinity,
intrisic activity

- DIRECT
- INDIRECT

NONSPECIFIC - NONRECEPTOR

- physical
- chemical
- binding to macromolecules of the organism which do not serve physiologically as receptors

(e.g. influence on ion channel, proton pump, modification of DNA, substrate inhibition of enzyme, binding to cell components, ...)

Non-receptor Mediated Drug Effects

- Physical
- Chemical
- **Metabolic pathways** (beyond the receptor)
  - **changes of ion channel permeability**
  - **changes of proton pump funtioning,**
  - **DNA modification,**
  - **substrate enzyme inhibition,**
  - **binding to cell components**

Biological Effect ∝ [DR]

$$D + R \Rightarrow DR$$

D: Drug or endogenous ligand

R: Receptor

DR: Drug-Receptor Complex

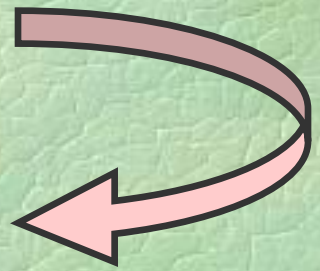
What is a Receptor?

- The term **"*receptor*"** specifically refers to proteins that participate in intracellular communication via chemical signals

- Upon recognition of an appropriate chemical signaling molecule ***("ligand"),*** receptor proteins transmit the signal into a biochemical change in the target cell

- Ligands include ***drugs*** as well as ***endogenous signaling molecules*** such as e.g. hormones and neurotransmitters

Drug binding in the organism } proteins



receptor – modulation of activity

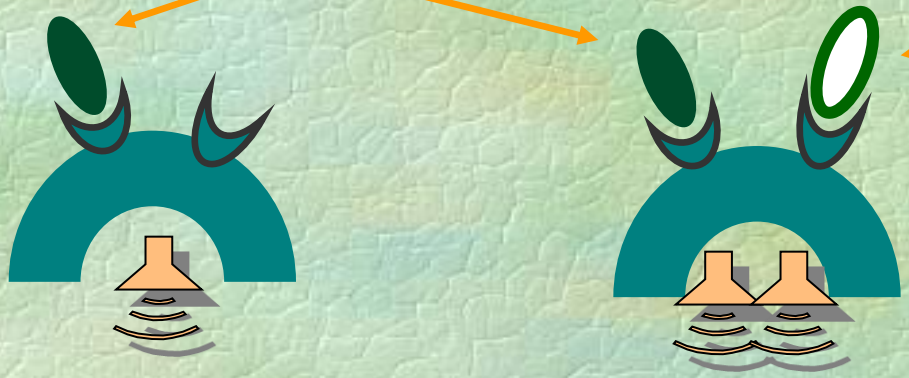
ion channel – modulation of permeability

enzyme – false substrate (abnormal metabolite;
inhibition of the function;
activation of a "pro-drug")

transporter –false substrate; inhibition

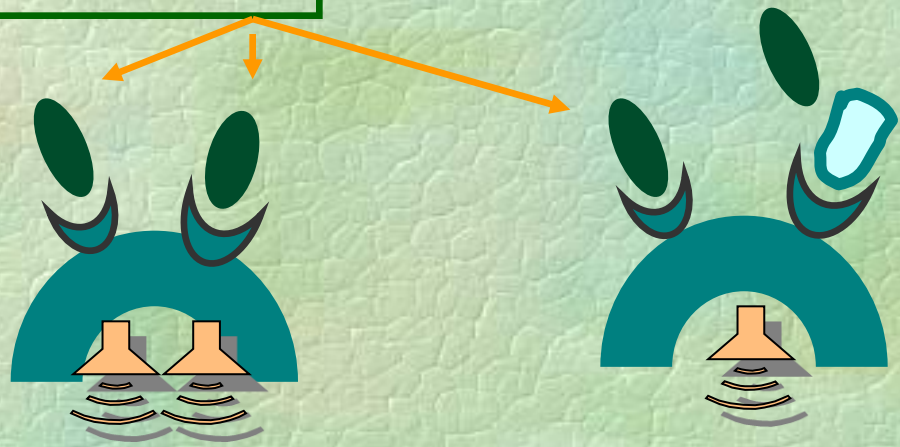
endogenous ligand = agonist

drug = agonist



endogenous ligand = agonist

drug = antagonist



TYPES of RECEPTOR LIGANDS

agonist

has

affinity (ligand)

has

intrinsic activity

antagonist

has

affinity (ligand)

has no

intrinsic activity

Major Receptor Families

- Ligand-gated ion channels (ionotropic r.)
- G protein–coupled receptors (metabotropic r.)
- Enzyme-linked receptors
- Intracellular receptors

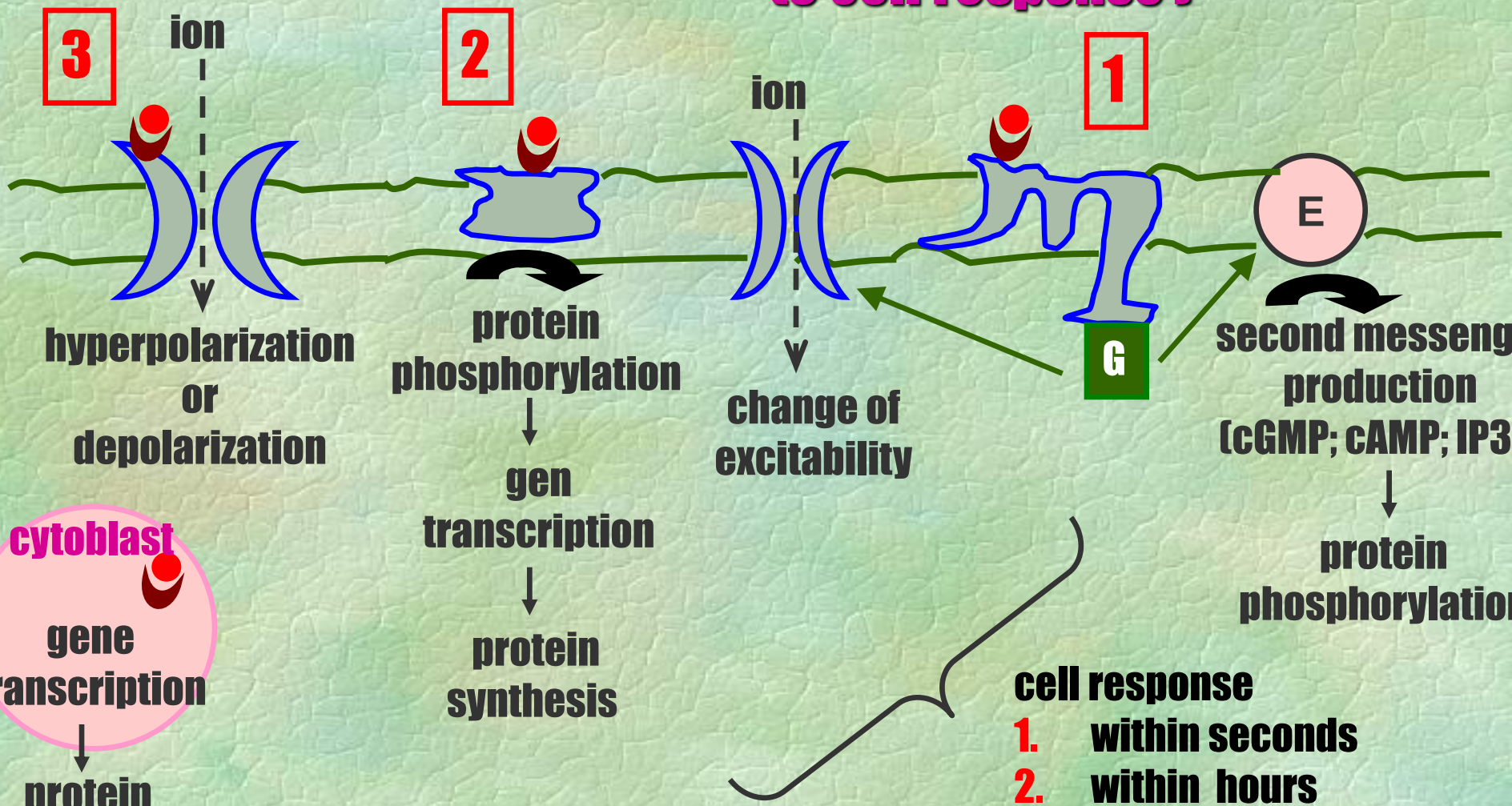
Examples:

~Nitric oxide (NO)

~Steroid (e.g., estradiol, progesterone, testosterone)

Receptor type	Receptor	Drug	Effects, treatment
MEMBRANE:			
1. G-protein coupled (metabotropic)	β2 adrenergic	salbutamol	asthma bronch.
2. enzyme coupled	insulin	insulin	diabetes mell.
3. ion channel (ionotropic)	$GABA_A$	muscimol	hallucinogen
CYTOSOLIC :			
4. Cytosol (intracellular r.)	DNA	intercalator (inserts itself into the DNA structure)	cancer

RECEPTOR SIGNAL TRANSDUCTION (from intrinsic activity to cell response)

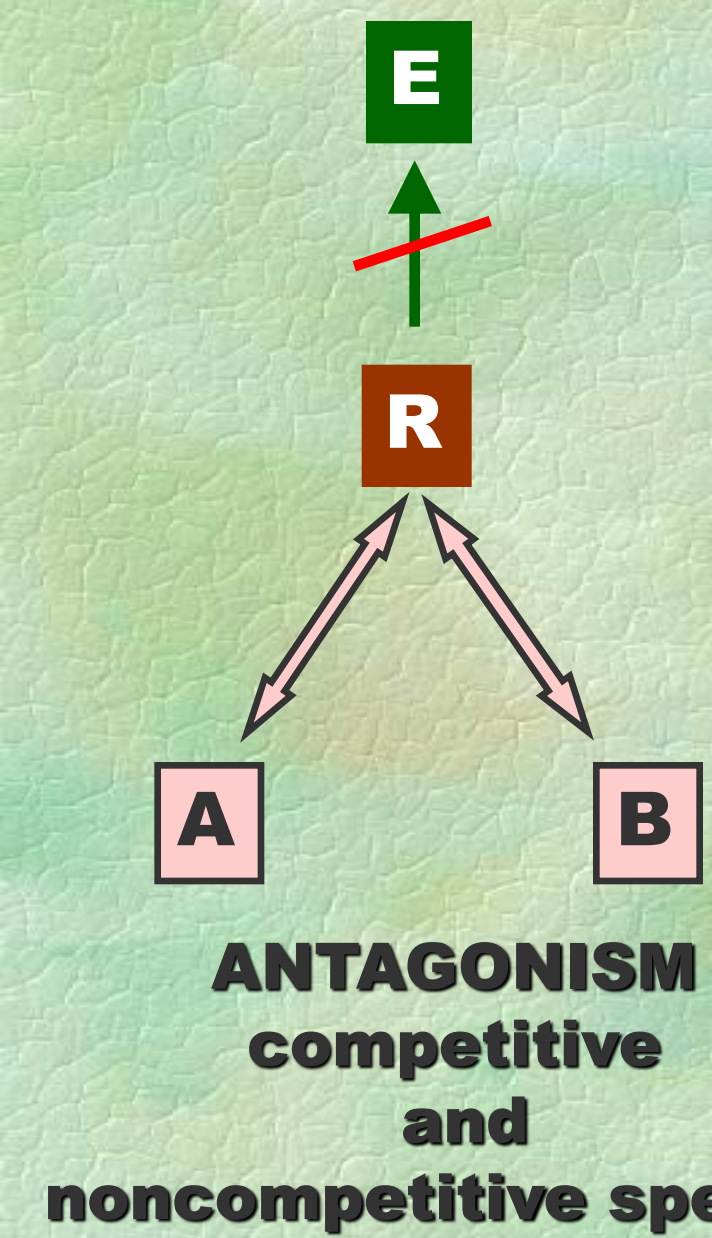


TYPES OF RECEPTOR LIGANDS

agonist

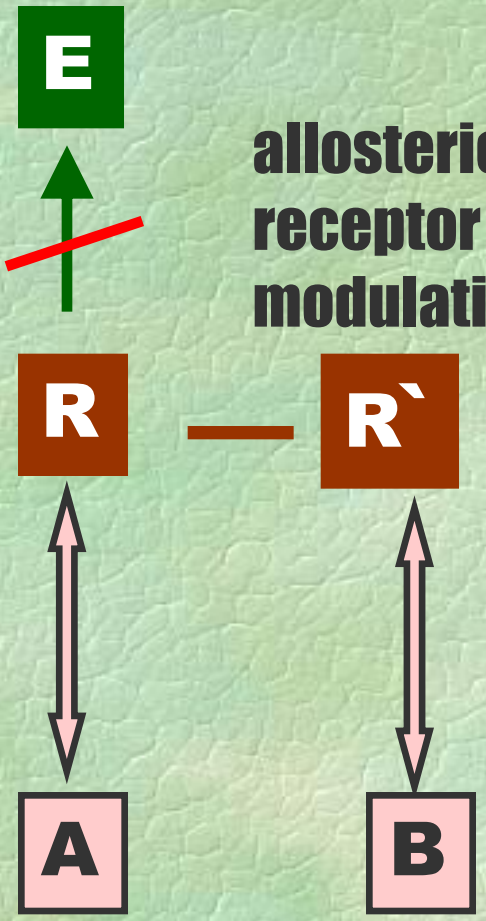
partial agonist (competitive dualist)

antagonist
- **competitive**
- **noncompetitive**
  - **specific**
  - **nonspecific**



A = agonist

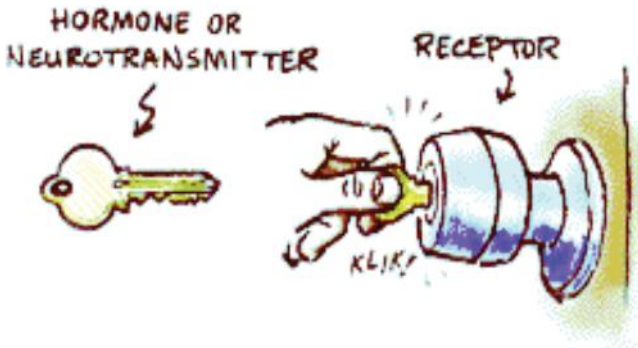
B = antagonist



ANTAGONISM
competitive
and
noncompetitive specific

ANTAGONISM
noncompetitive
nonspecific

The Lock and Key Model of Ligand-Receptor Interaction



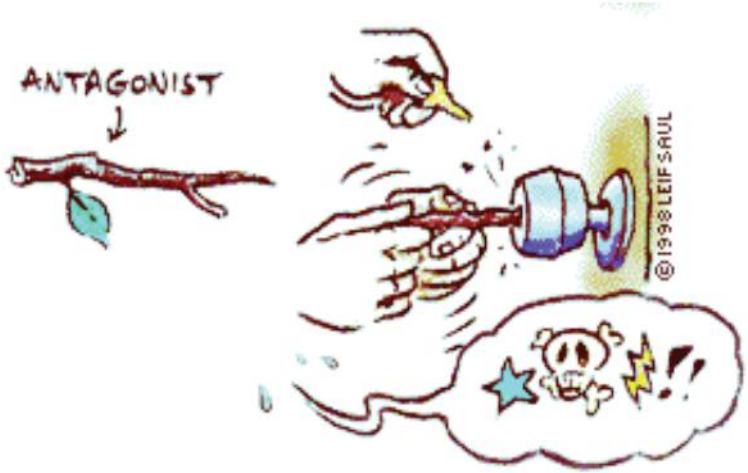
-a ligand such as a hormone or neurotransmitter (the "**key**") bind to specific receptors (the "**lock**")

-this binding "unlocks" the cell's response.

-many drugs work by mimicking a naturally occurring hormone or neurotransmitter

-if the drug causes the receptor to respond in the same way as the naturally occurring substance, then the drug is referred to as an **agonist**

-these are drugs that can "pick the lock".



-other drugs work in the opposite way - as **antagonists**.

-these drugs bind to the receptor, but do not produce a response.

-because the drug prevents the receptor from binding to the normal hormone or neurotransmitter, it has an inhibitory effect on the naturally occurring substance.

TYPES OF RECEPTOR LIGANDS

agonist

partial agonist (competitive dualist)

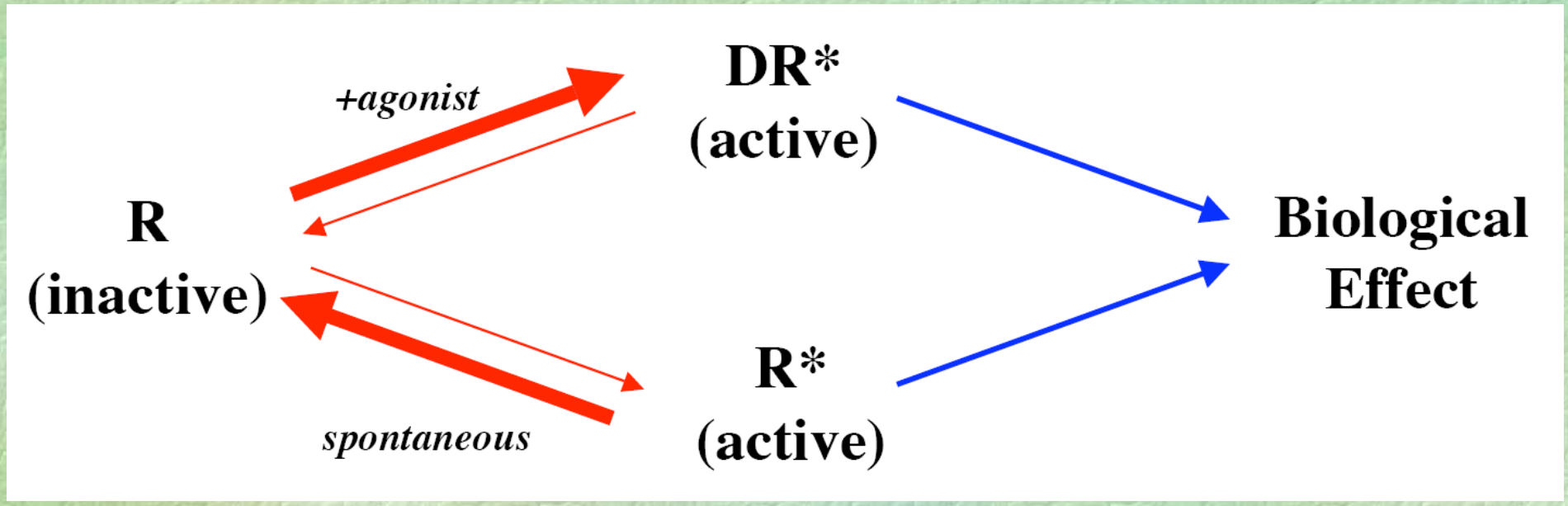
antagonist
- competitive
- noncompetitive
  - specific
  - nonspecific

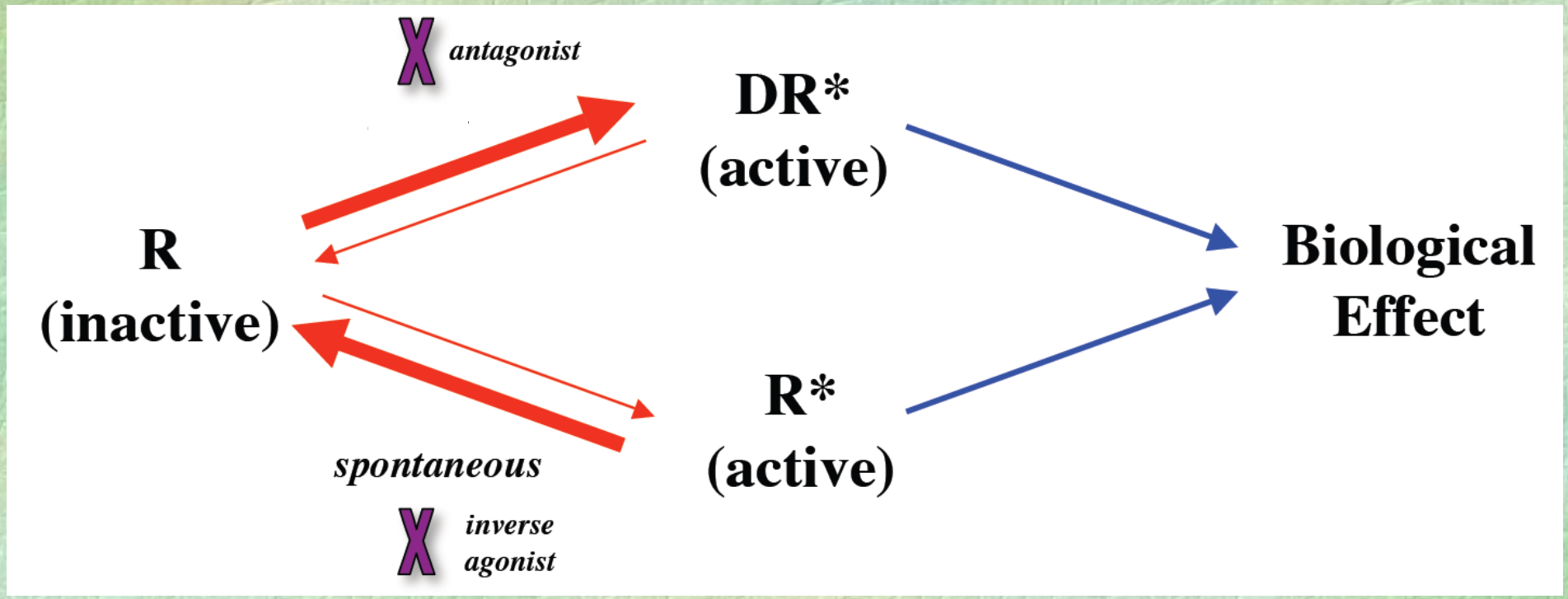
inverse agonist

partial inverse agonist

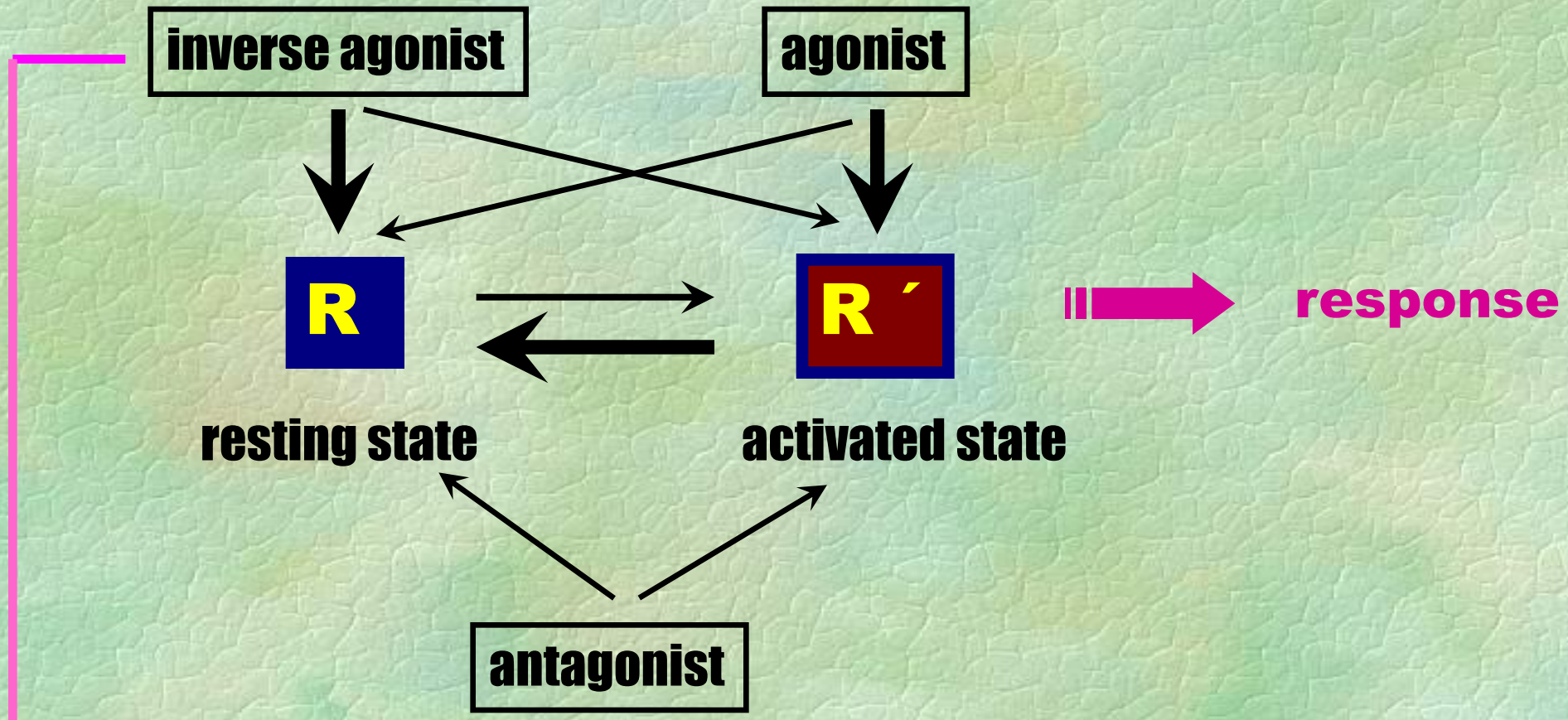
Quantitative model of receptor influence = the "two-state model"

In some of receptors systems , even in the absence of an endogenous ligand or an exogenously administered agonist, there is intrinsic activity ("tone")
- there is an inherent stability of constitutively activated receptors.


+agonist
DR*
(active)
R
(inactive)
Biological
Effect
R*
(active)
spontaneous


antagonist
DR*
(active)
R
(inactive)
Biological
Effect
R*
(active)
spontaneous
inverse
agonist

Quantitative model of receptor influence = the "two-state model"



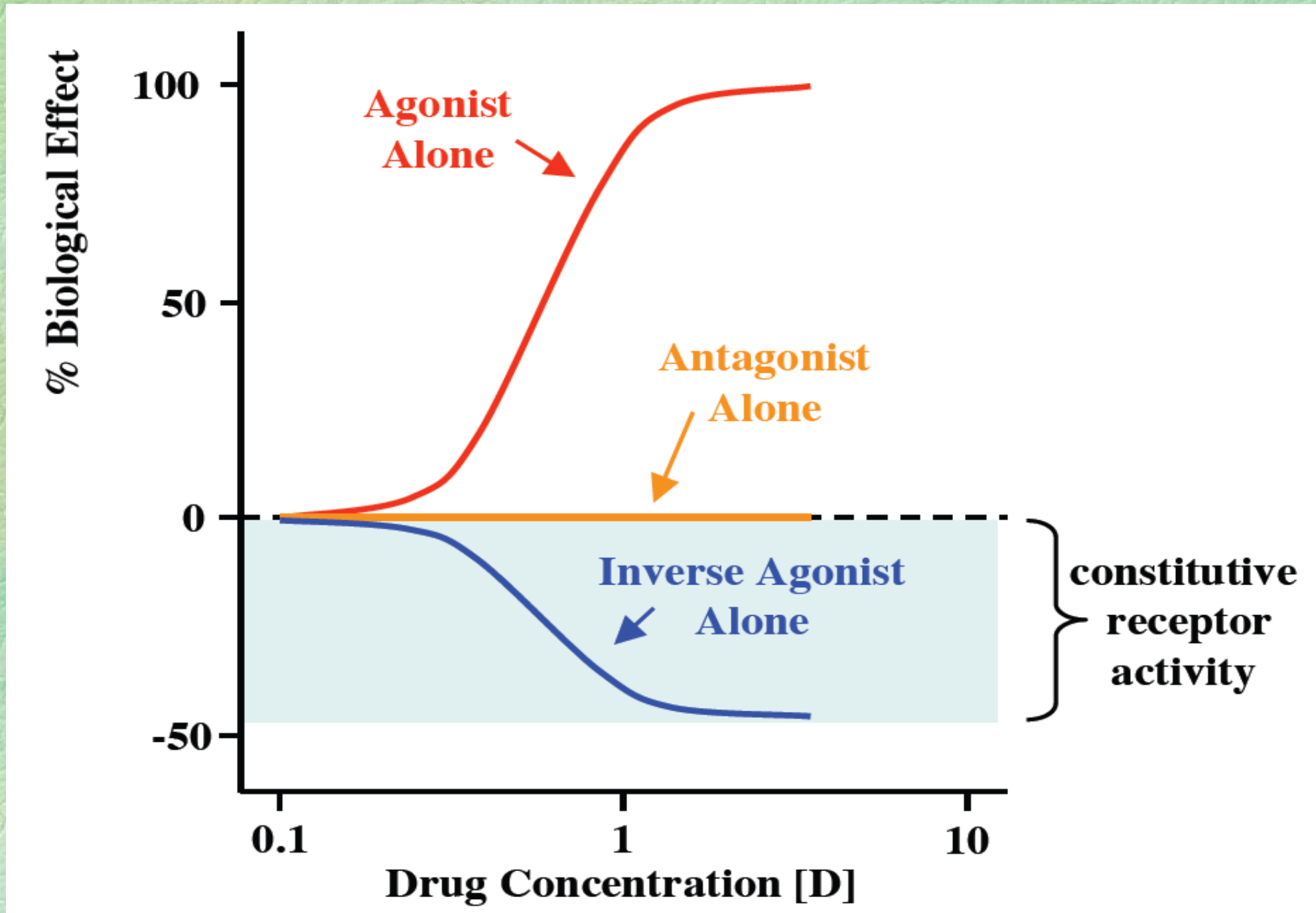
acts by abrogating the intrinsic activity of the free (unoccupied) receptors

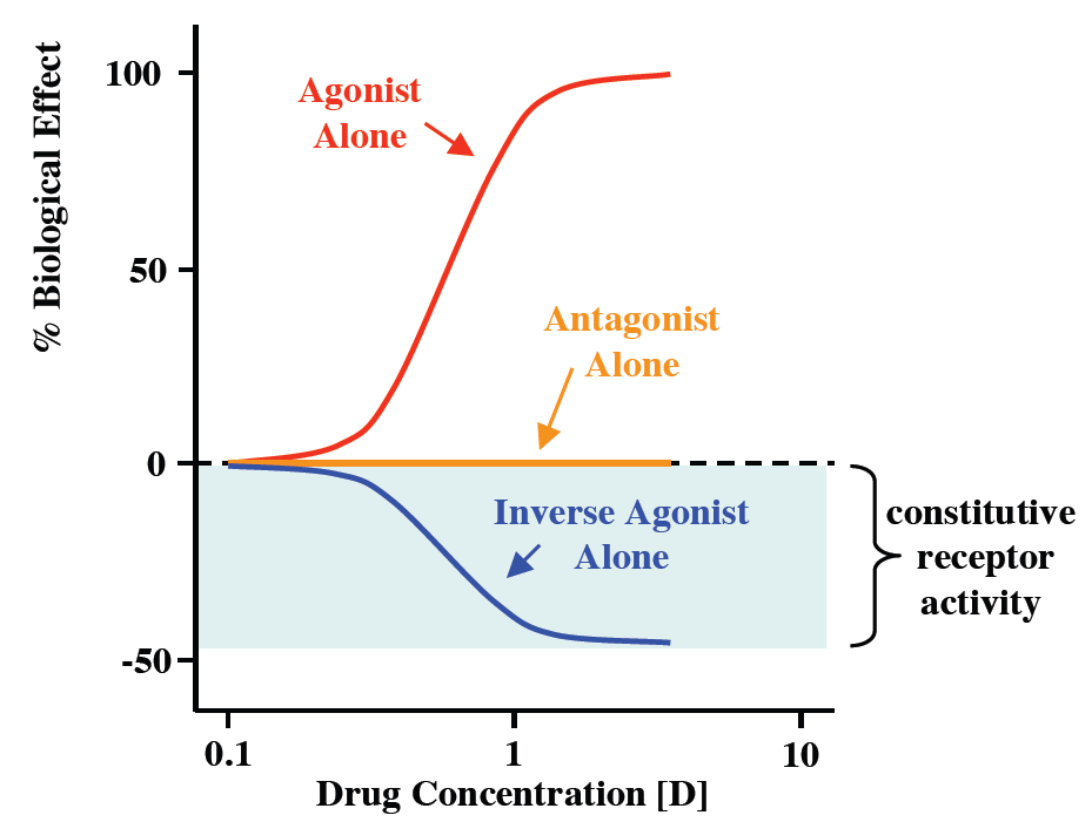
agonists ... stabilize R*

partial agonists ... stabilize R + R*

inverse agonists ... stabilize R

competitive antagonist ... prevent full, partial, and inverse agonists from binding to the receptor


% Biological Effect
100
50
0
-50
Agonist
Alone
Antagonist
Alone
Inverse Agonist
Alone
constitutive
receptor
activity
0.1
1
10
Drug Concentration [D]



Agonist

- has an independent impact upon receptor activity

Antagonist

- impacts receptor activity only in the presence of agonist

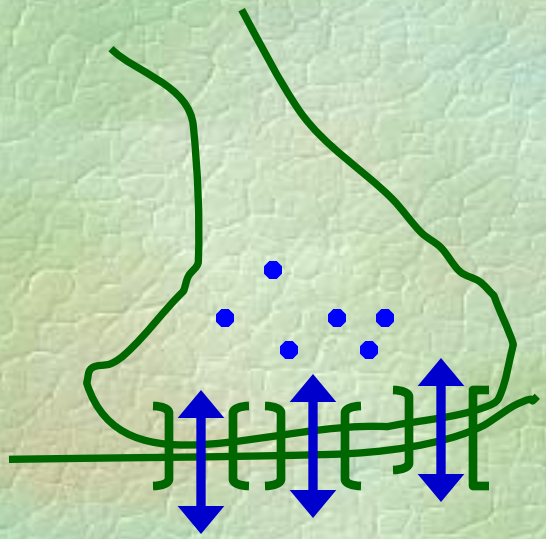
Inverse Agonist

- has an independent impact upon receptor activity
- produces an effect opposite to agonist

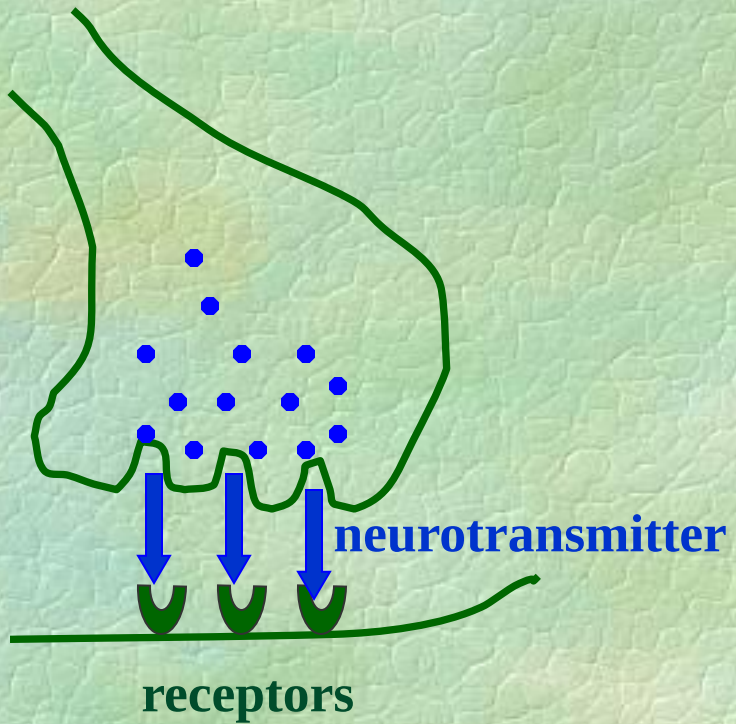
AGONISTIC LIGANDS	ACTION
agonist	maximal receptor activation
partial agonist	receptor activation but not maximal
inverse agonist	inactivation of constitutively active receptors

ANTAGONISTS	ACTION
competitive	reversible receptor blockade
noncompetitive (specific)	irreversible receptor blockade
noncompetitive (nonspecific, allosteric)	reversible or irreversible binding to site other than active site of receptor

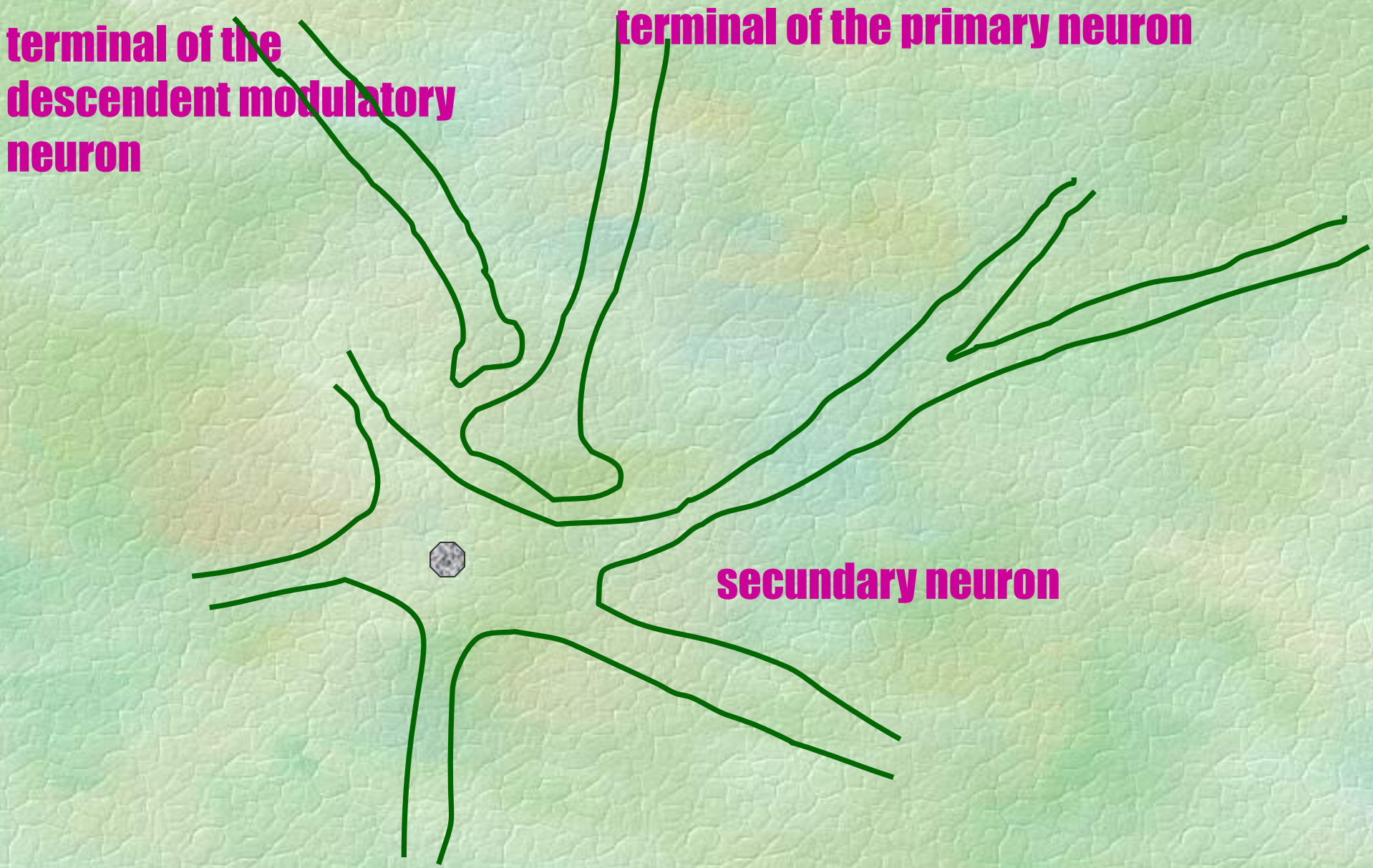
SYNAPSE

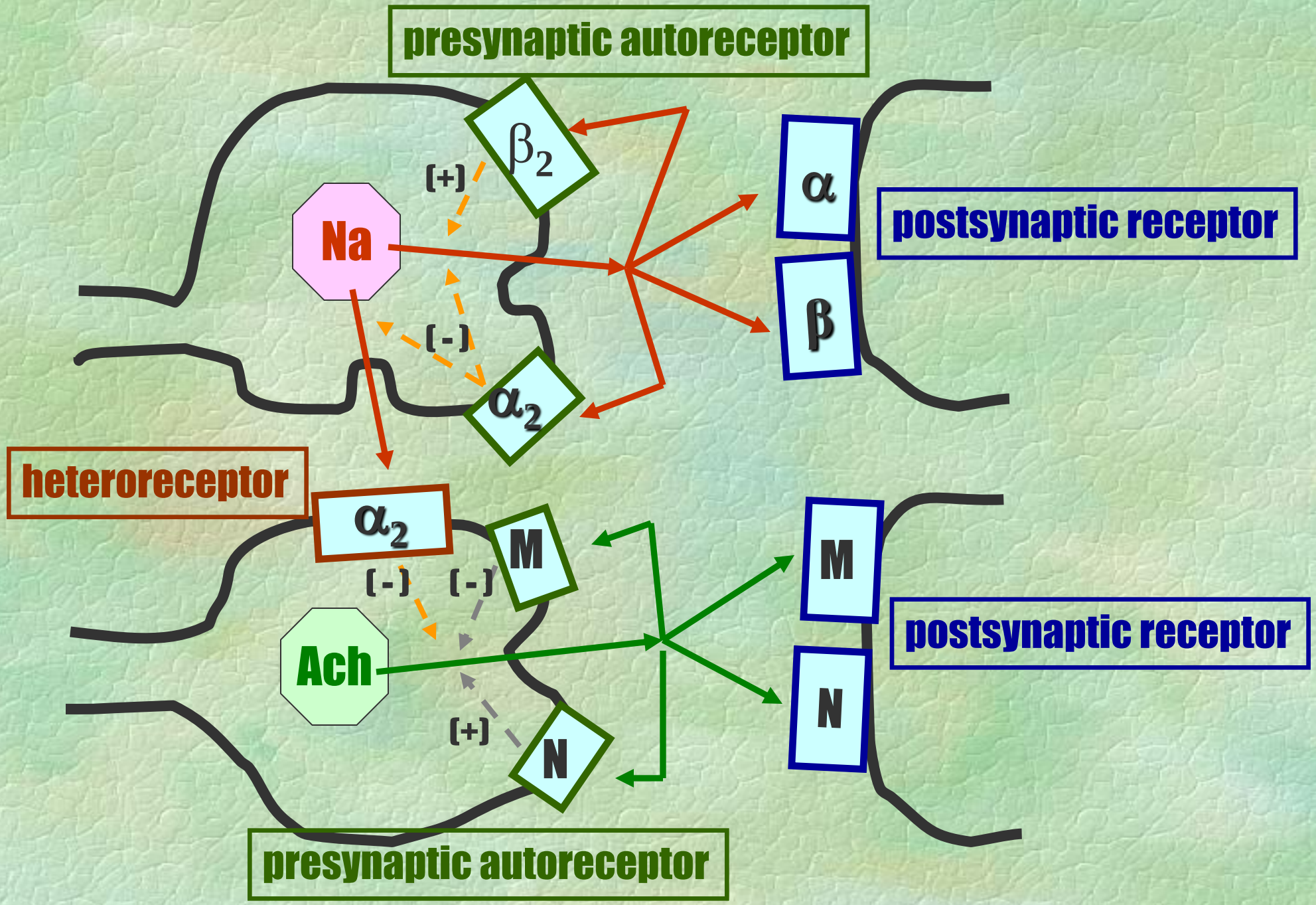


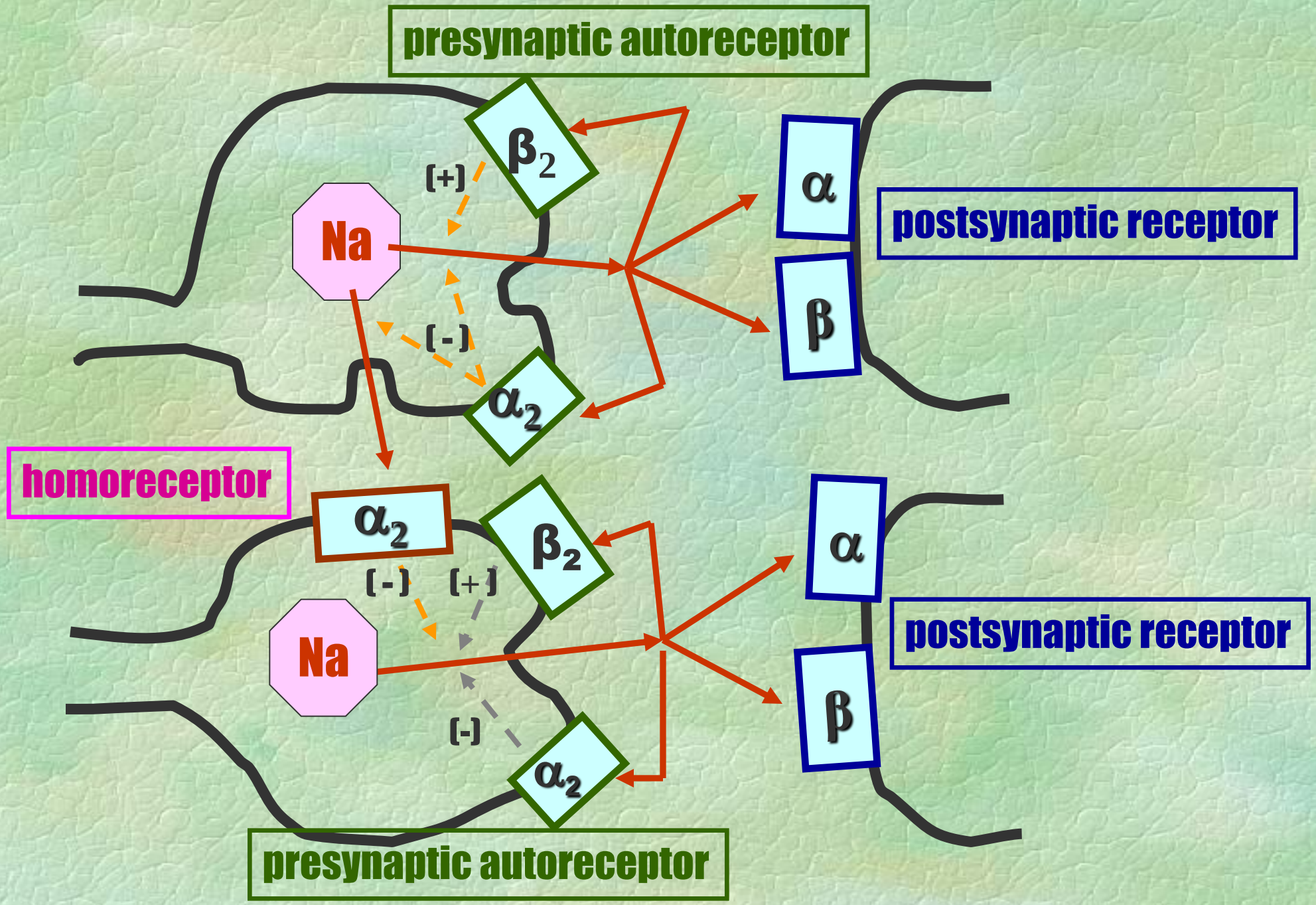
electric
("gap junction")



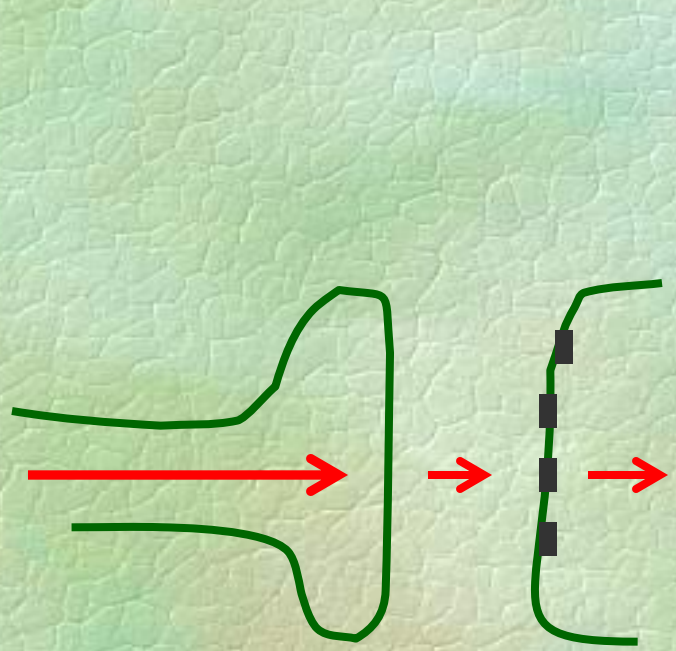
chemic

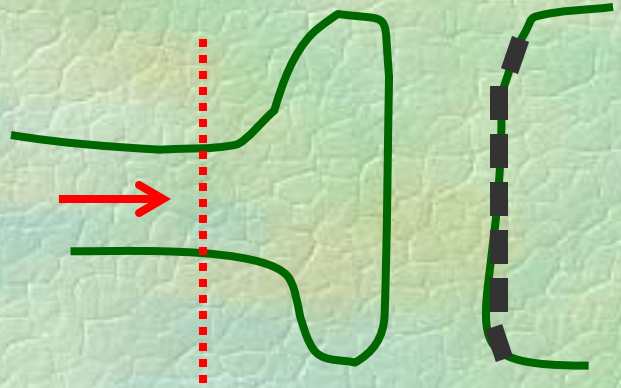

terminal of the descendent modulatory neuron
terminal of the primary neuron
secundary neuron


presynaptic autoreceptor
β2
[+]
Na
[-]
α2
α
β
postsynaptic receptor
heteroreceptor
α2
[-]
[-]
M
Ach
[+]
N
M
N
postsynaptic receptor
presynaptic autoreceptor

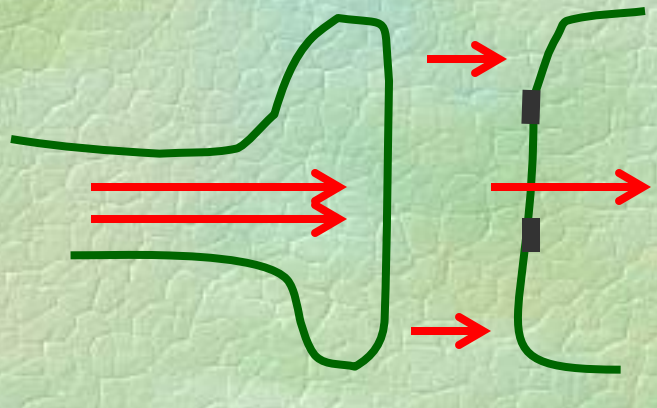

presynaptic autoreceptor
β2
[+]
Na
α
β
postsynaptic receptor
[-]
α2
homoreceptor
α2
β2
[-]
[+]
Na
α
β
postsynaptic receptor
[-]
α2
presynaptic autoreceptor

chronic antagonist influence





receptor
“up-regulation”



receptor
“down-regulation”

chronic agonist influence

Mechanisms of drug effects

SPECIFIC - RECEPTOR MEDIATED

DRUG ⟺ RECEPTOR

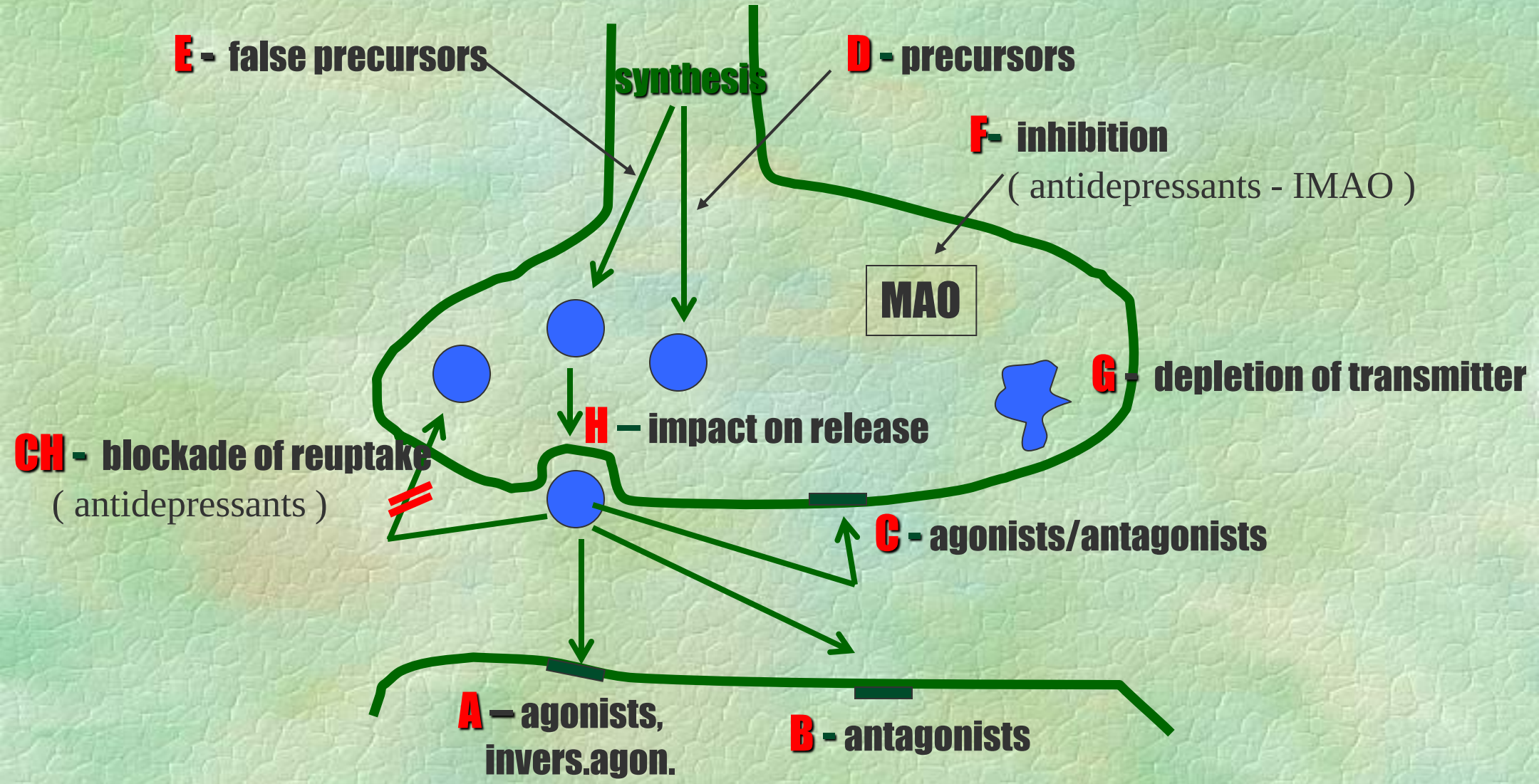
affinity,
intrisic activity

- DIRECT
- INDIRECT

NONSPECIFIC - NONRECEPTOR

- physical
- chemical
- binding to macromolecules of the organism which do not serve physiologically as receptors

(e.g. influence on ion channel, proton pump, modification of DNA, substrate inhibition of enzyme, binding to cell components, ...)



Drug effects on synapse function

→ DIRECT - A, B, C

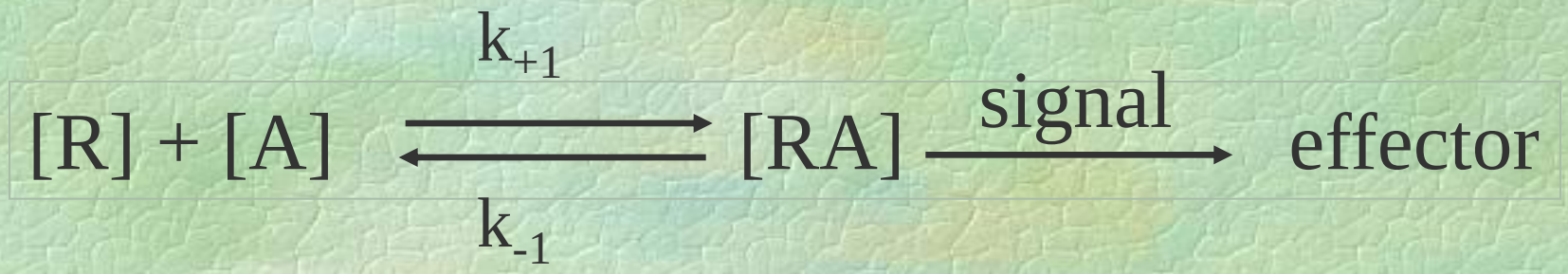
→ INDIRECT - D, E, F, G, H, CH

Beneficial *versus* Toxic Drug Effects

Paracelsus 1493-1541
(the father of toxicology)

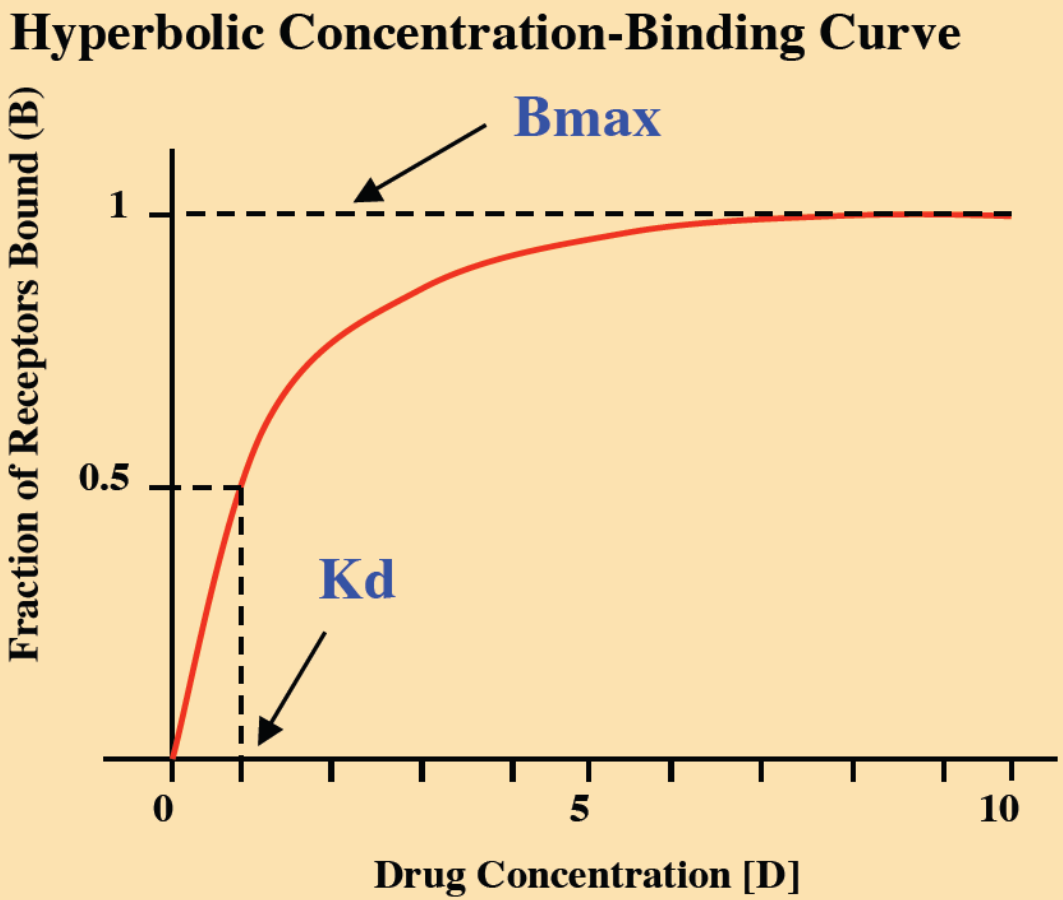
"all things are poison and not without poison; only the dose makes a thing not a poison"

- it is not the nature of the drug that determines toxicity, but rather the amount
- everything, in excess, is potentially toxic



R = receptor
A = drug "A"
RA = complex receptor/drug
k_{+1} = association constant
k_{-1} = dissociation constant
effectors = molecules of transduction of the drug/receptor interaction into changes of cell activity
(e.g. adenylylcyclase)

Relationship of Drug Concentration and Receptor Binding



$$B = \frac{B\max \times [D]}{[D] + Kd}$$

B - Fraction of available receptors bound

Bmax -Maximal binding of receptors (=1)

[D] - Concentration of drug

Kd - Equilibrium Dissociation Constant

- Drug concentration at which 1/2 of available receptors are bound

- Measure of **affinity** of drug/receptor interaction

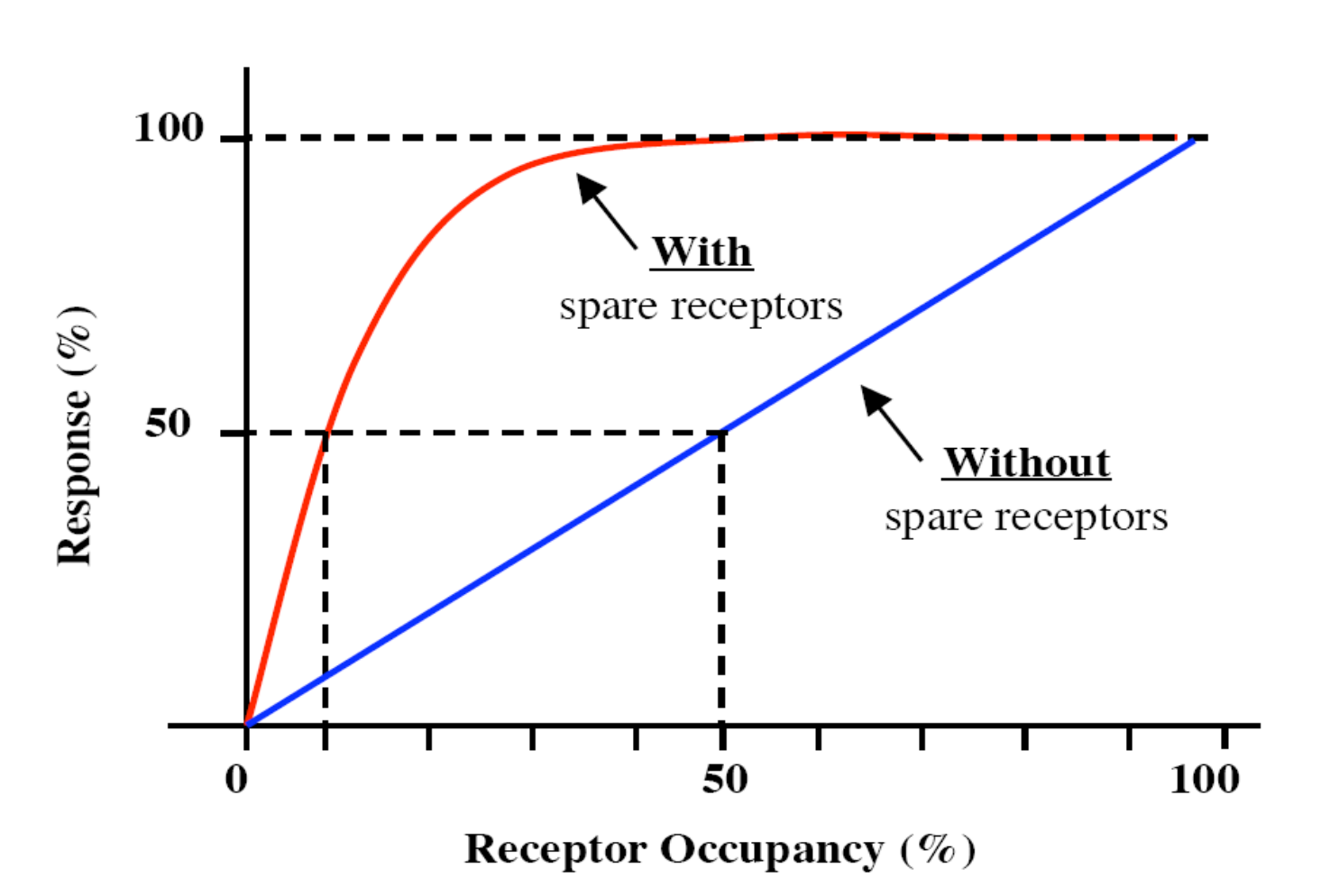
Spare Receptors

- In some systems, full agonists are capable of eliciting 50% response with less than 50% of the receptors bound (receptor occupancy)
- Pool of available receptors exceeds the number required for a full response
- Common for receptors that bind hormones and neurotransmitters

At equilibrium: $$\frac{[D][R]}{[DR]} = K$$

  - if [R] is increased, the same [DR] can be achieved with a smaller [D]
  - a similar physiological response is achieved with a smaller [D]

Receptor Occupancy versus Biological Response



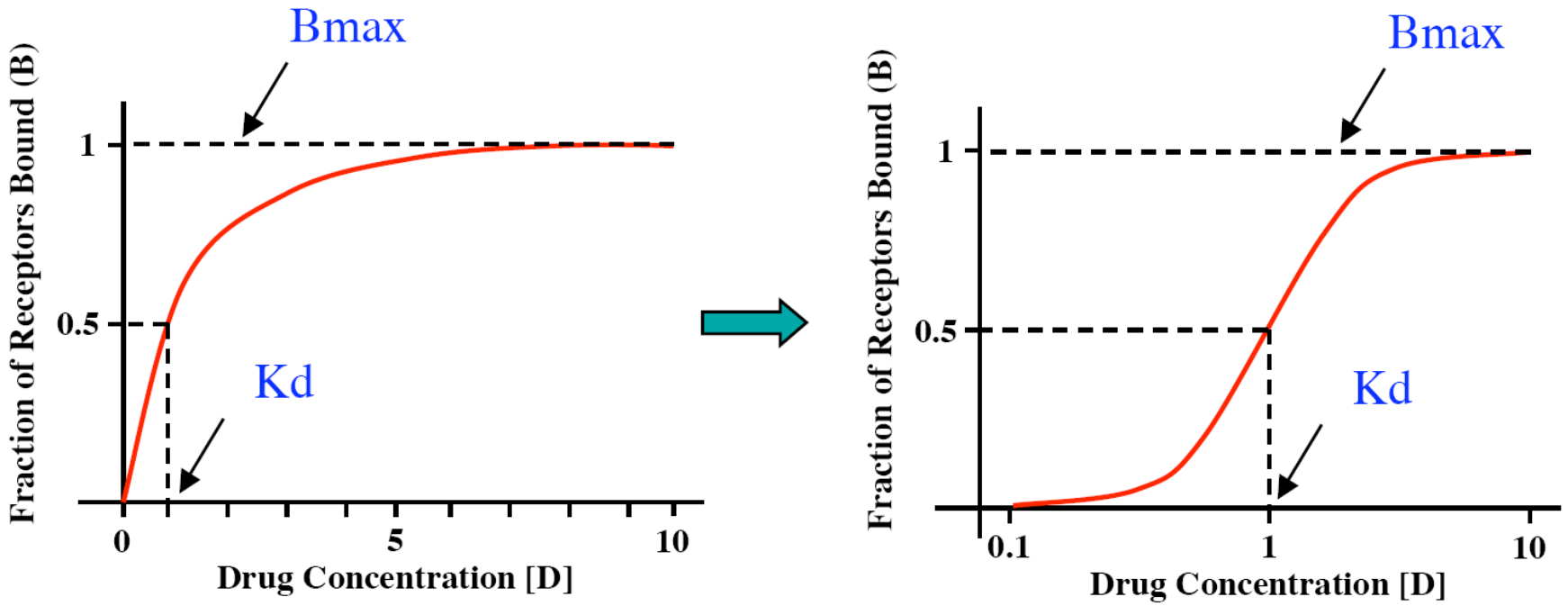
Without spare receptors:

- *50% response = 50% occupancy*
- *Biological effect is proportional to [DR] at all drug concentrations*

With spare receptors:

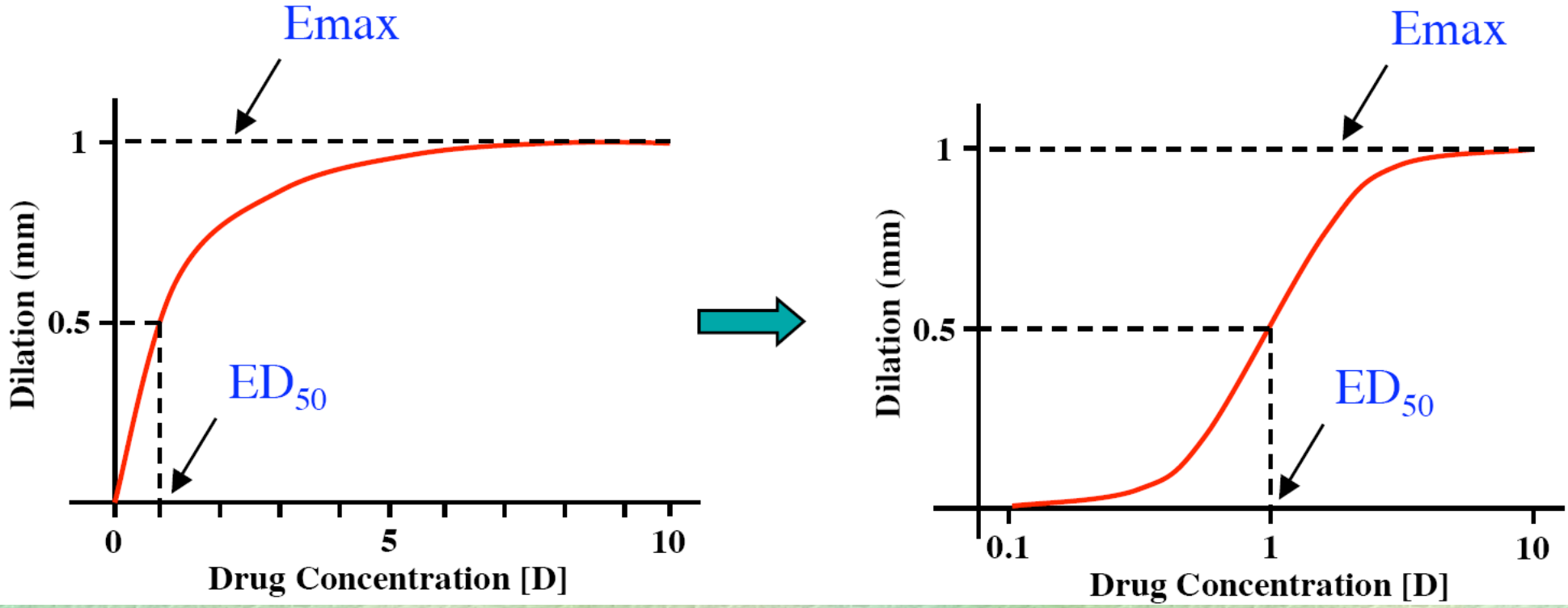
- *50% response = 10% occupancy*
- *Biological effect is proportional to [DR] only at low drug concentrations*

Sigmoidal Receptor Binding Curves



- Semi-logarithmic transformation (Common representation of pharmacological data)
- Expands concentration scale at low concentration
  (where binding is changing rapidly)
- Compresses concentration scale at high concentrations
  (where binding is changing slowly)
- Does not change value of Bmax and Kd

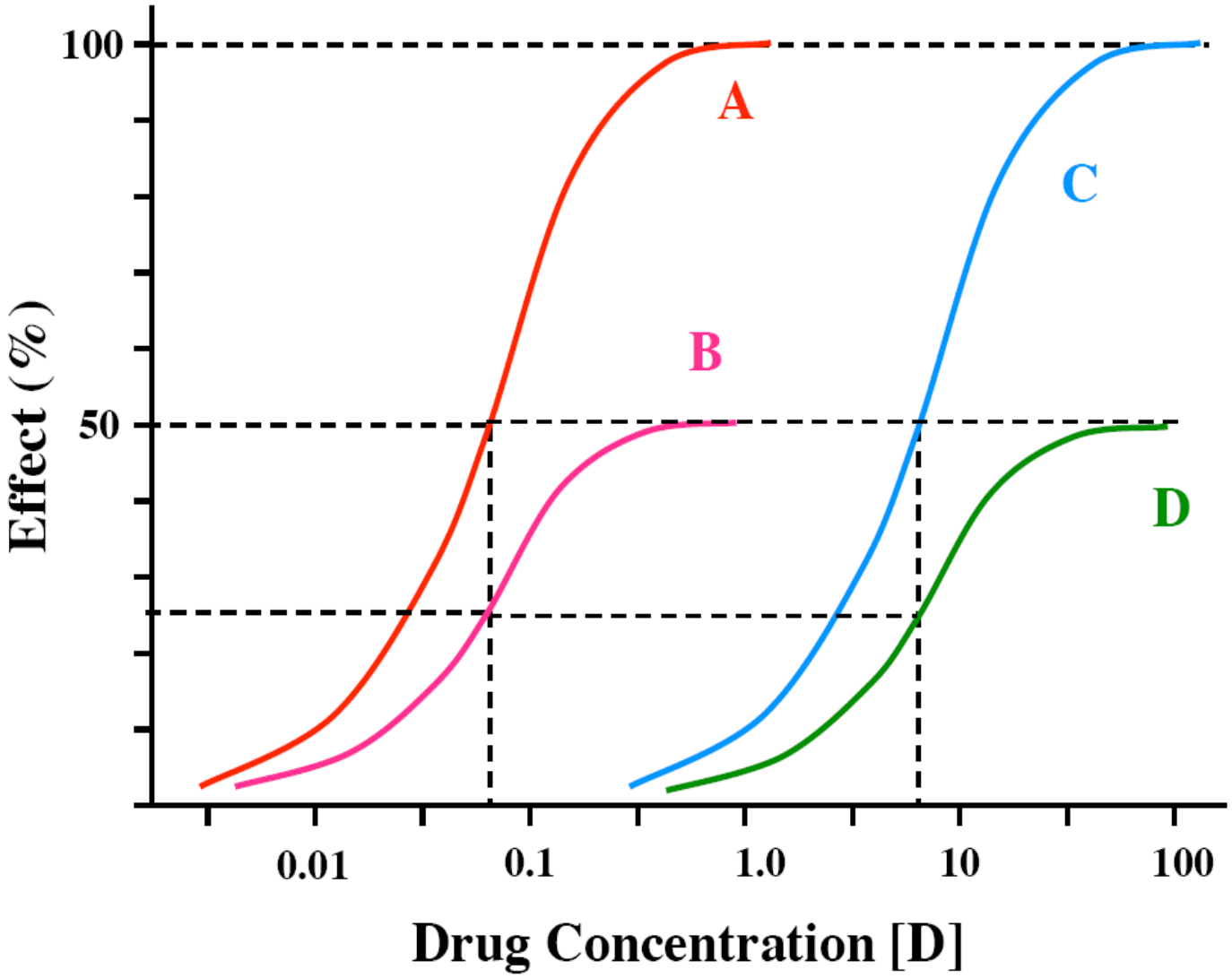
Graded Dose-Response Curves



Emax - the maximum response achieved by an agonist -also referred to as drug **efficacy**

ED_{50} - the drug concentration (or dose) at which 50% of Emax is achieved - also referred to as drug **potency**

Agonist Types: Its All Relative



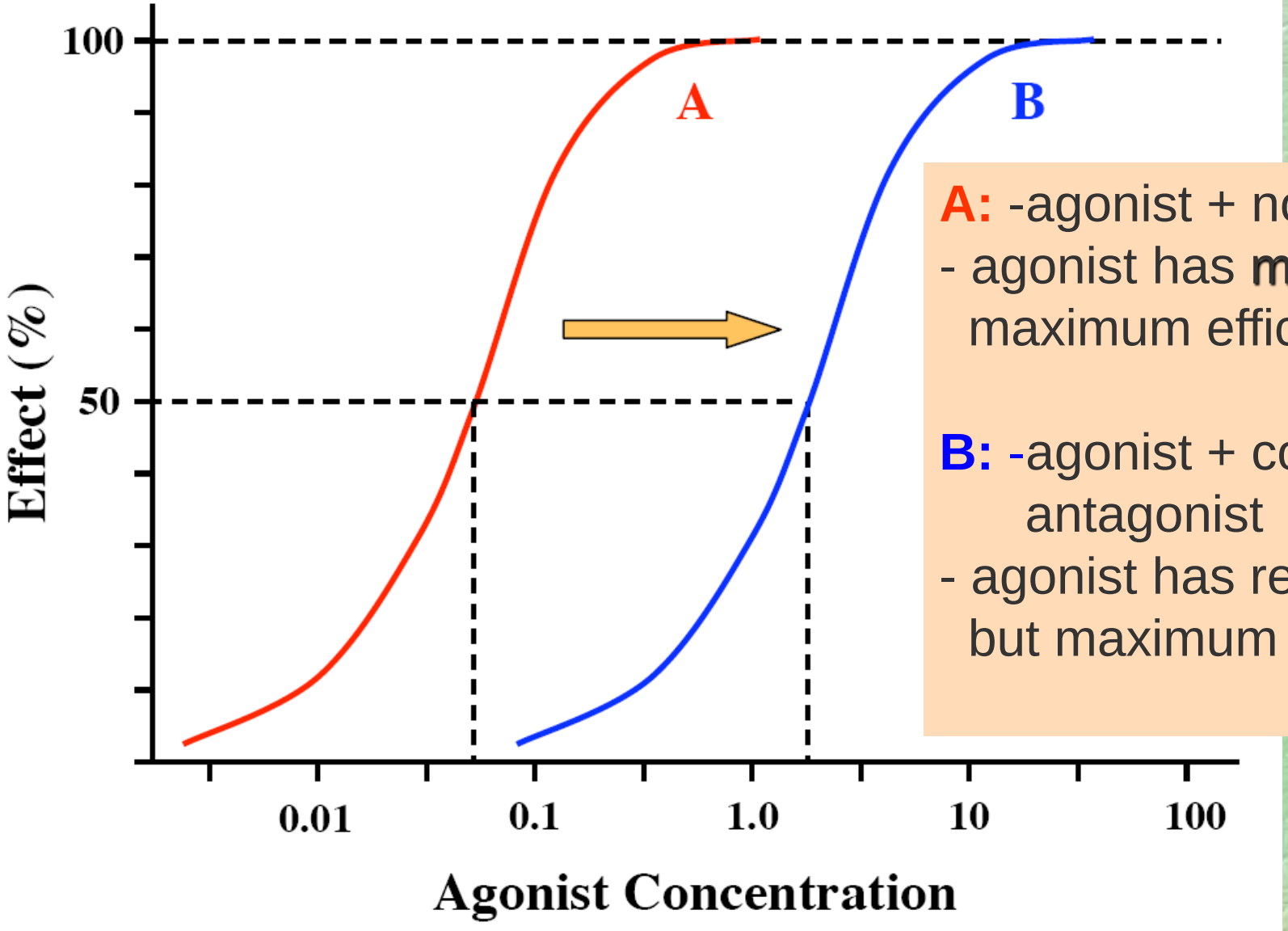
A: **full agonist**
maximum potency,
maximum efficacy

B: **partial agonist**
maximum potency,
reduced efficacy

C: **full agonist**
reduced potency,
maximum efficacy

D: **partial agonist**
reduced potency,
reduced efficacy

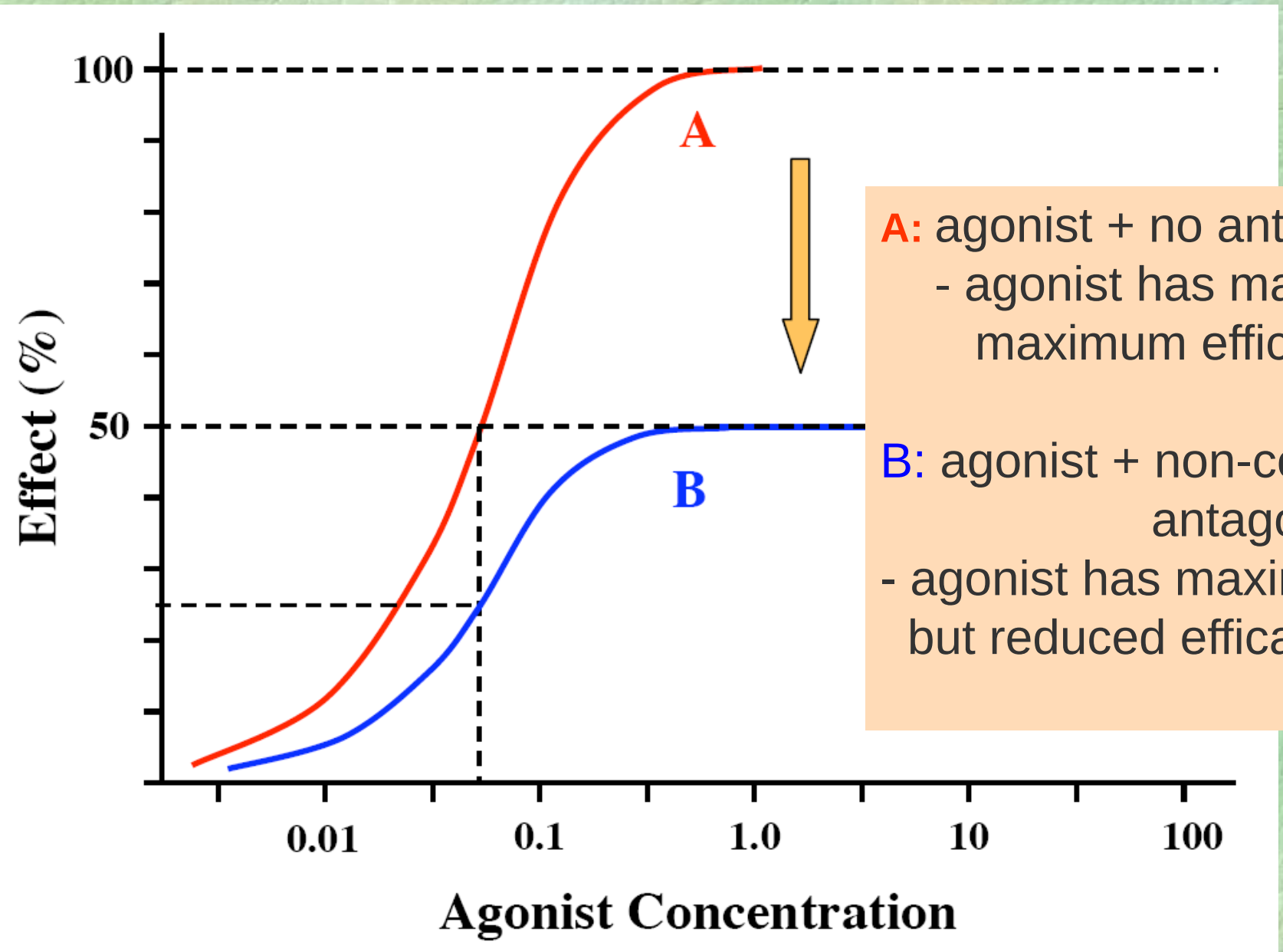
Competitive Antagonists - Effect on Dose Response Curves



A: -agonist + no antagonist
- agonist has **maximum** potency, maximum efficacy

B: -agonist + competitive antagonist
- agonist has reduced potency, but maximum efficacy

Non-Competitive Antagonists - Effect on Dose Response Curves

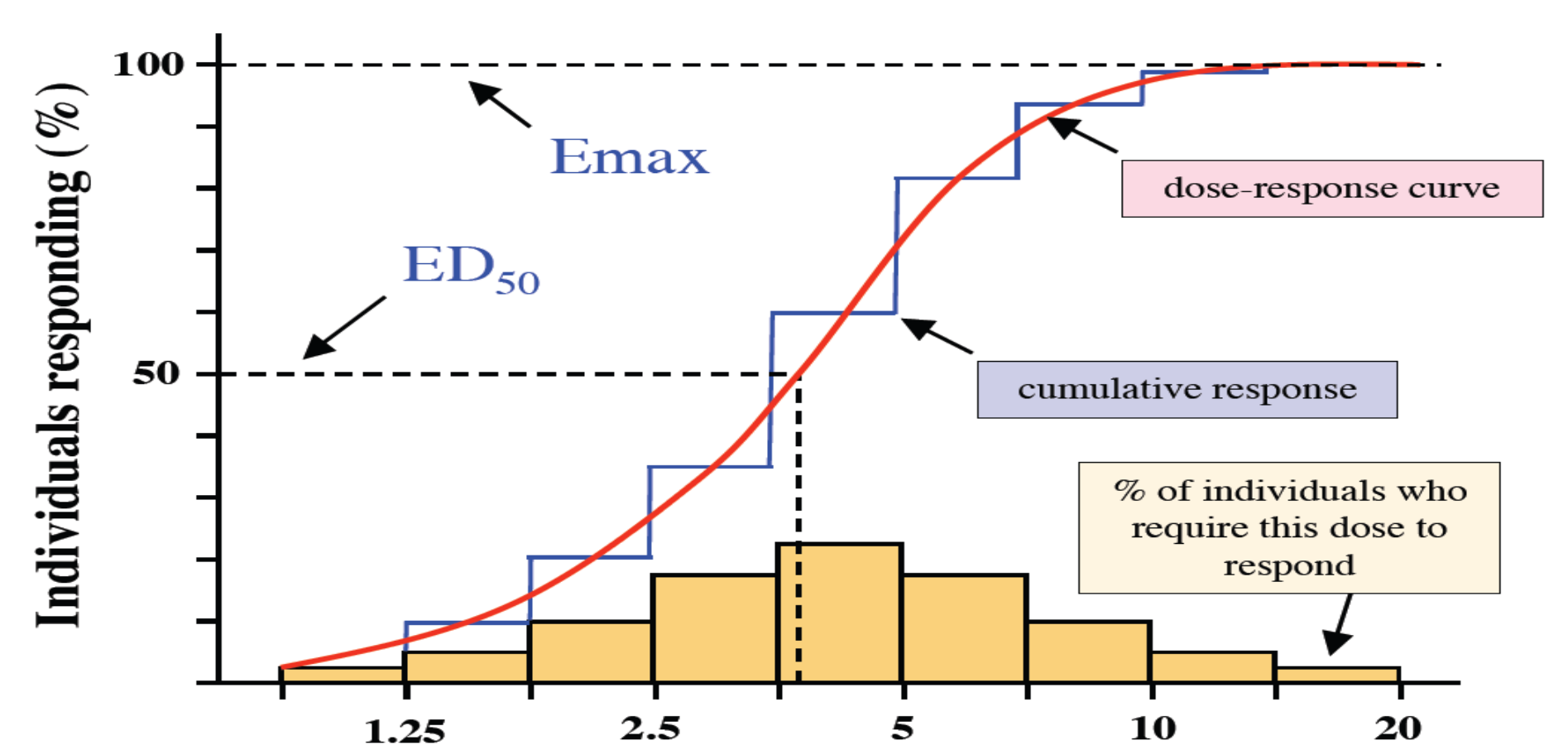


A: agonist + no antagonist
- agonist has maximum potency, maximum efficacy

B: agonist + non-competitive antagonist
- agonist has maximum potency, but reduced efficacy

Quantal Dose-Response Curves

Quantal Phenomena: - all-or-none



- describe population rather than single individual responses to drugs
- based on plotting cumulative frequency distribution of responders against the log drug dose