Chap 1. Basic principles of neuropharmacology

The scientific study of the effects of drugs on the nervous system

Focusing on the actions of drugs for treatments and of abuse

Use drugs as tools for better understanding of normal nervous system functioning

Information about drugs and their mechanism of action

Development of safer and more effective treatment

Drugs

Antidepressant
Antianxiety: minor tranquilizers
Anticonvulsant
Antipsychotic: major tranquilizers
Common drugs: side effects to the CNS
Common substances affecting the CNS: caffeine, alcohol, nicotine
Addictive substances: stimulants, depressants, hallucinogens

How drugs work?

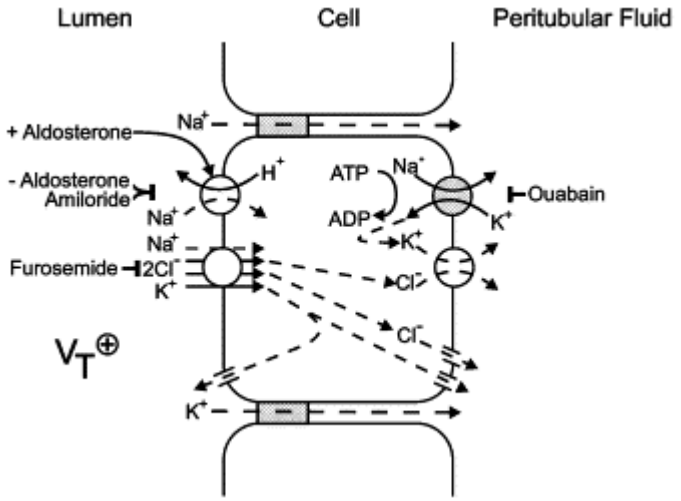
Drugs affecting nervous system
Drugs affecting other organ systems

Brain drugs manifest more complicated actions: drug-induced neural plasticity

- Molecular action
- Intra- & inter-cellular action
- Brain circuitry: structure and function

Example

- Fluoxetine: antidepressant targeting serotonin transporter
- Furosemide: diuretic drug targeting chloride ion channels in nephrons of the kidney



MiR-16 Targets the Serotonin Transporter: A New Facet for Adaptive Responses to Antidepressants. Science (2010) 329, 1537-1541.

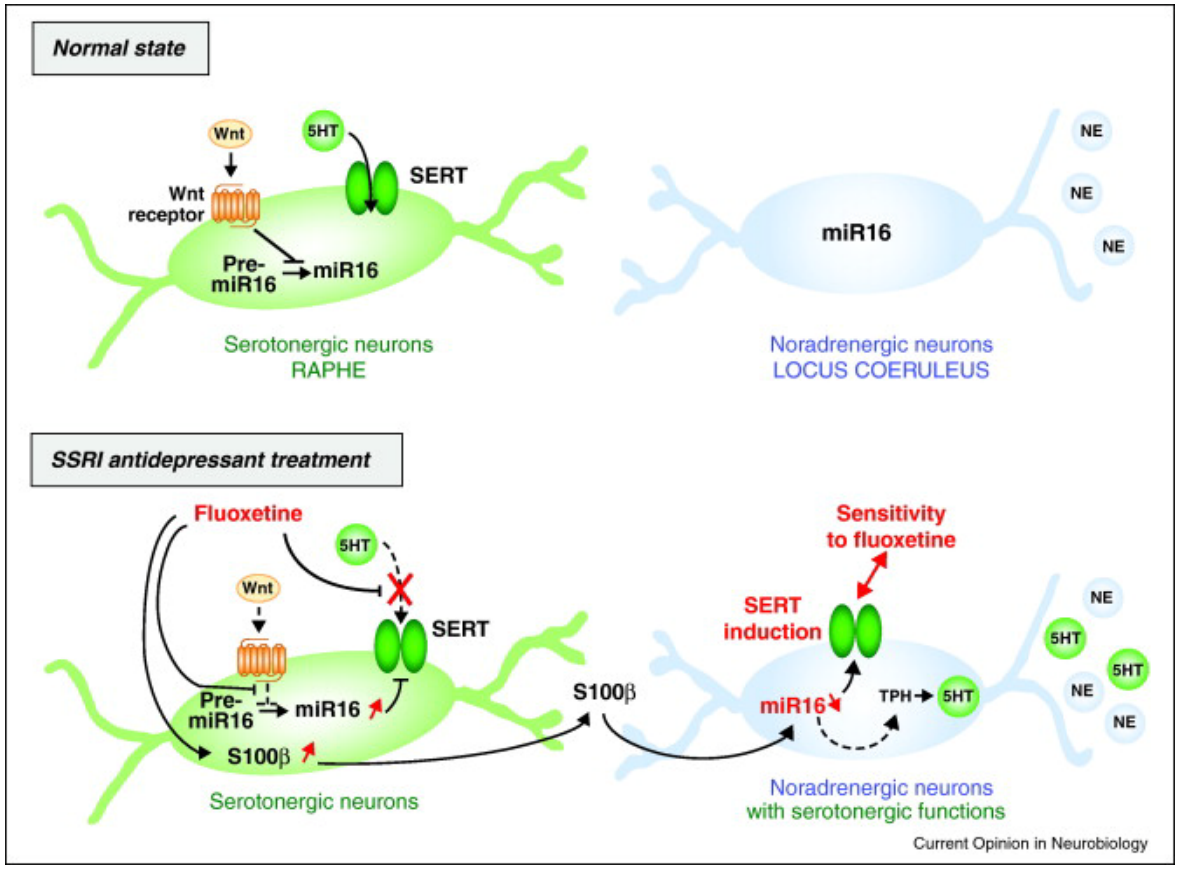


Figure 2. MiR-16 targeting SERT is a newcomer relaying the fluoxetine action in serotonergic and noradrenergic neurons. The high level of miR-16 prevents SERT expression in noradrenergic neurons. In addition to blocking the uptake of 5-HT by the SERT, fluoxetine increases miR-16 level by antagonizing the Wnt canonical pathway and induces the release of the neurotrophic factor S100β in the raphe. S100β acts on the locus coeruleus by decreasing the level of miR-16, which unlocks the expression of SERT as well as the onset of others serotonergic markers as tryptophan hydroxylase (TPH) in noradrenergic cells. The locus coeruleus becomes a new source of 5-HT in the brain under SSRI fluoxetine treatment. Current Opinion in Neurobiology. Volume 21, Issue 6, December 2011, Pages 858–865

Drugs as tools to probe brain function

Neurotransmitters:

- Identification
- Elucidation of synthesis, degradation, receptors
- Via using synthetic and plant substances

Neurotransmitter receptors

- Subtypes: multiple receptors for a neurotransmitter
- Development of selective drugs

Recognition of complex postreceptor signal transduction cascades

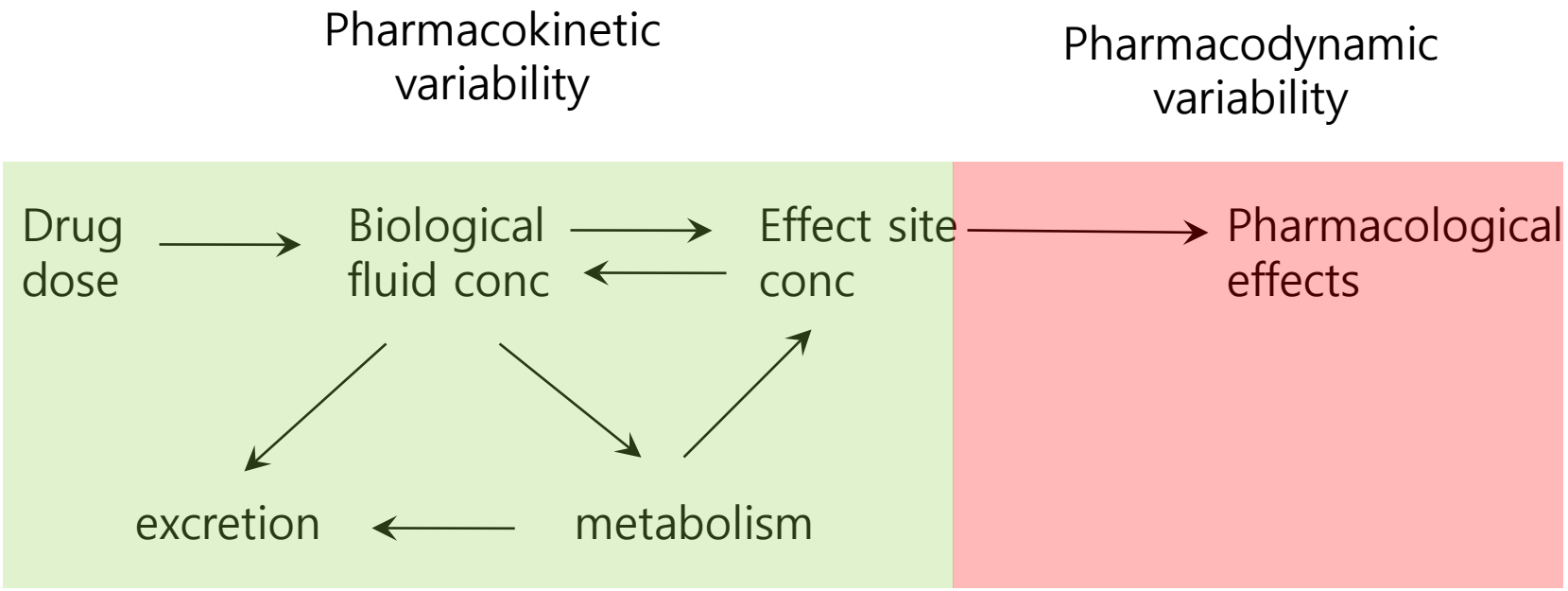
Functional study

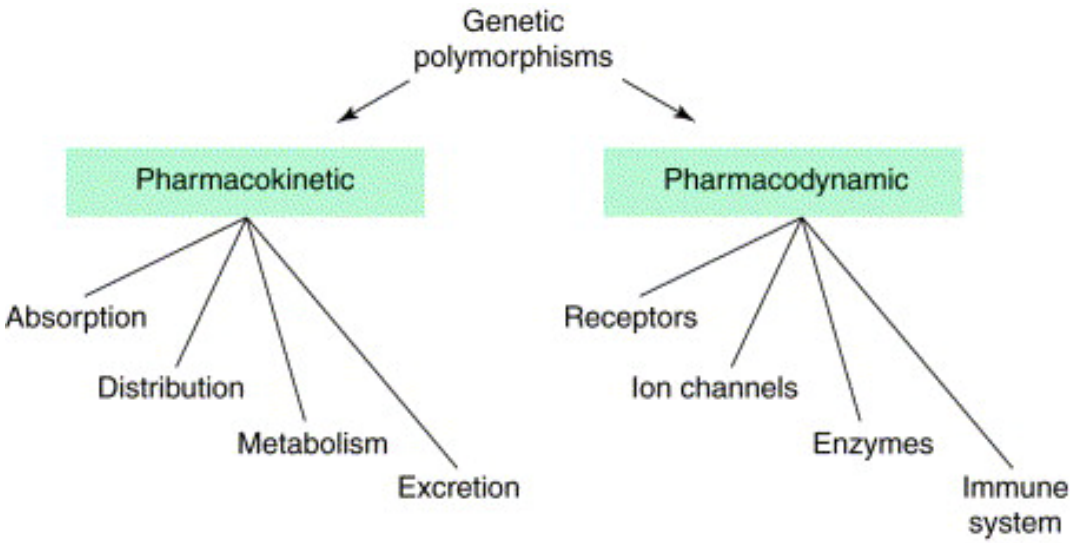
Principles of general pharmacology

Drug → organism

Absorption
Stability
Elimination
} pharmacokinetics

Drug action: pharmacodynamics (the underlying mechanism)





TRENDS in Pharmacological Sciences

Pharmacokinetics

Absorption

The route of administration

Oral

- absorption from gut
- binding to plasma proteins
- penetration through BBB
- penetration through cell membrane (intracellular target)

Peripheral:

- subcutaneous
- intraperitoneal
- Intravenous
- Intracerebroventricular
- Intracerebral

Stability

Metabolism to inactive congeners

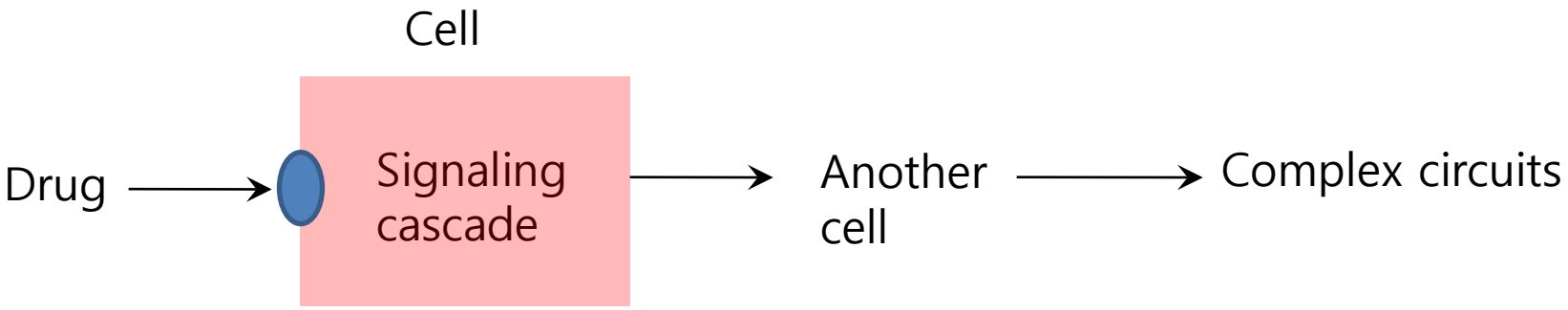
Elimination

Via urine, bile, exhaled air

Pharmacodynamics

The underlying mechanisms of drug action
(drug interaction with protein targets)

Drug binding (potency: affinity)
Drug efficacy
Dose-dependent drug response
Drug interaction with nonreceptor proteins

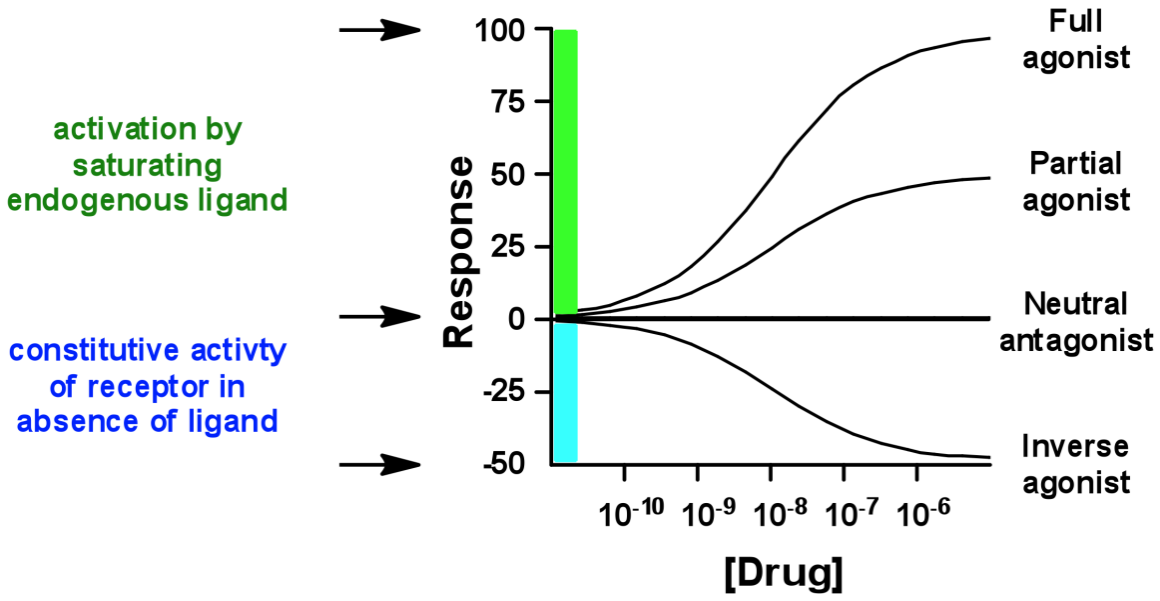


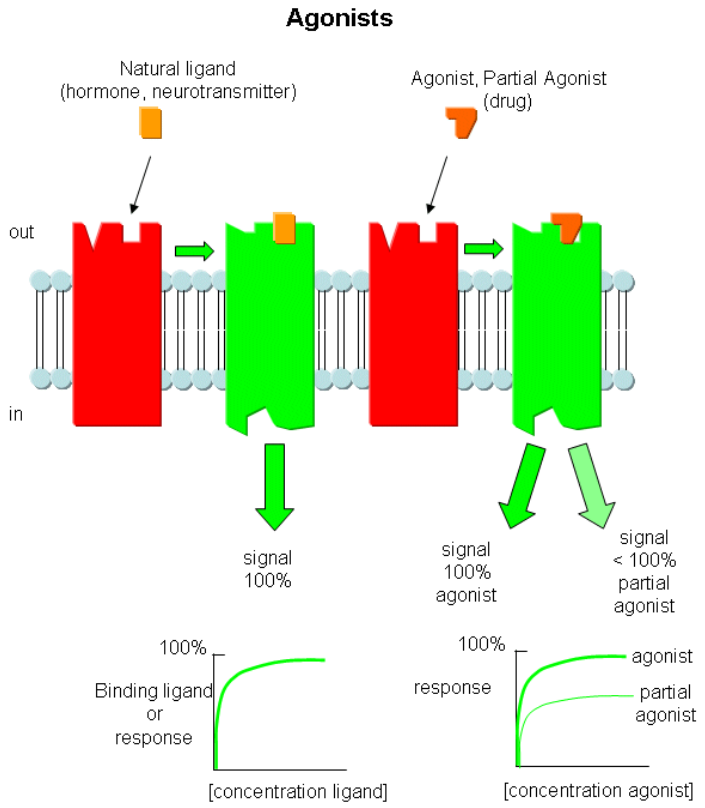
Drug binding

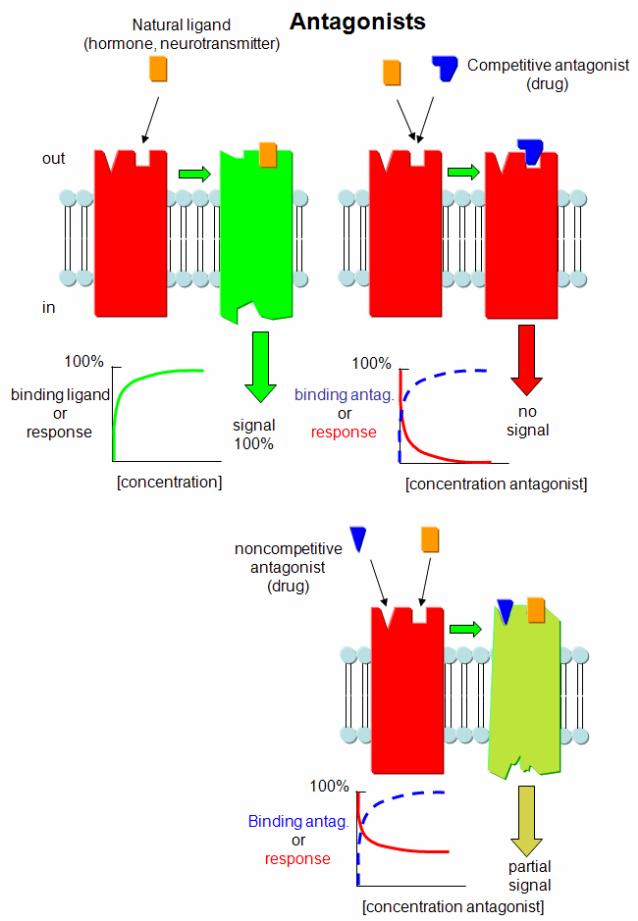
Ligands: endogenous or exogenous (drug)

4 types

- Agonist
- Partial agonist
- Antagonist
- Inverse agonist (require intrinsic basal activity)

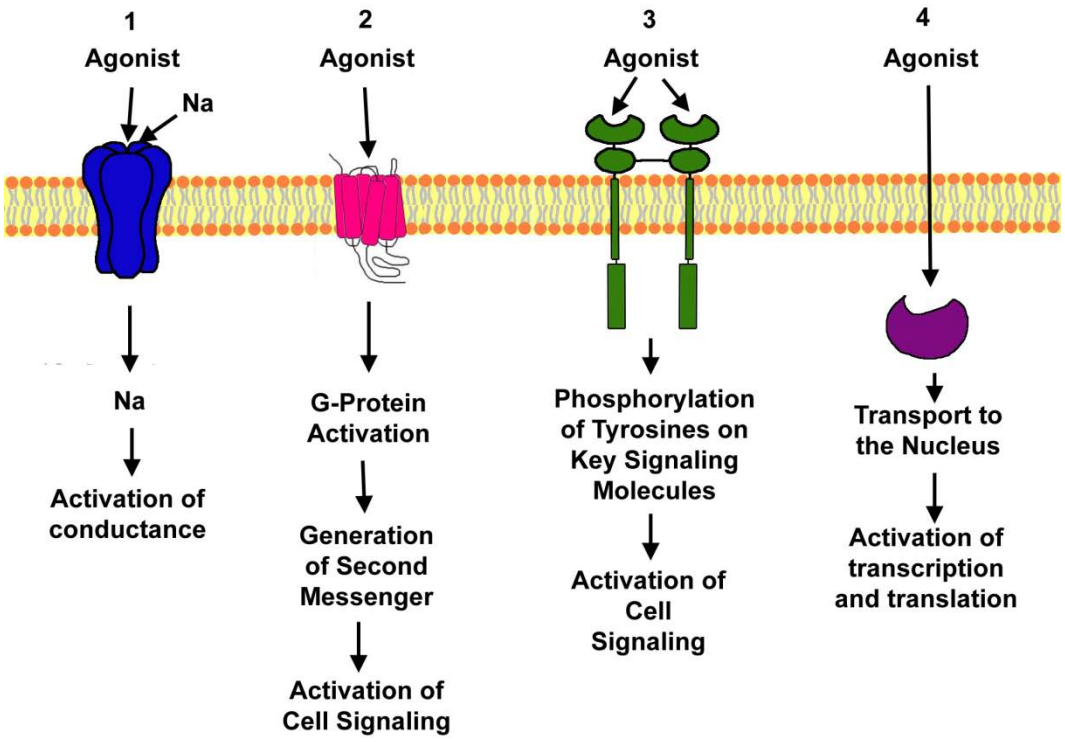



Agonists
Natural ligand
(hormone, neurotransmitter)
Agonist, Partial Agonist
(drug)
out
in
signal
100%
signal
100%
agonist
signal
< 100%
partial
agonist
100%
Binding ligand
or
response
[concentration ligand]
100%
response
agonist
partial
agonist
[concentration agonist]


Antagonists
Natural ligand
(hormone, neurotransmitter)
Competitive antagonist
(drug)
out
in
100%
binding ligand
or
response
signal
100%
[concentration]
100%
binding antag.
or
response
no
signal
[concentration antagonist]
noncompetitive
antagonist
(drug)
100%
Binding antag.
or
response
partial
signal
[concentration antagonist]

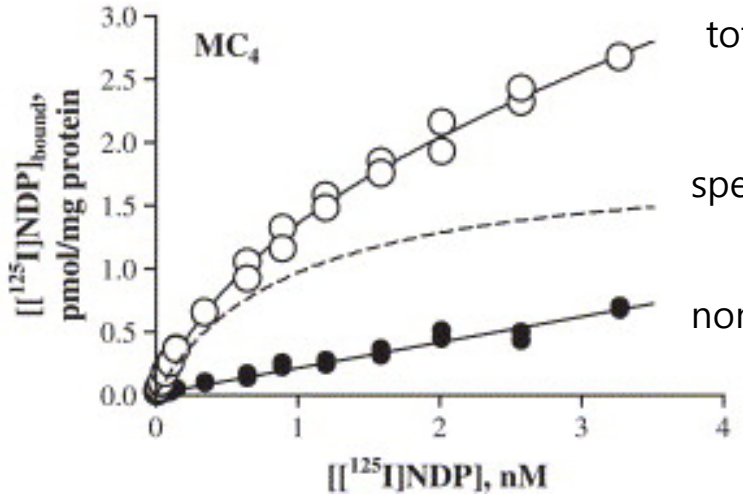
Receptors

G-protein coupled receptors (GPCRs)
Ion-channel linked receptors
Enzyme-linked receptors (tyrosine kinase)
Gene regulating receptors (steroid hormone receptors)



Drug-receptors interaction

3 major criteria to assess the resulting ligand binding
should be specific (stereoselective): specific target protein
should be saturable: finite amount of an individual target protein
should attain a steadystate (reversible binding)



total

specific (ideal): saturation curve

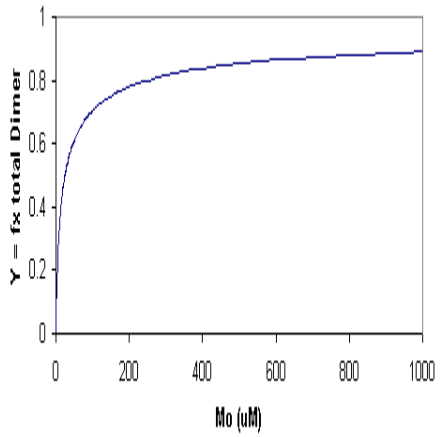
nonspecific

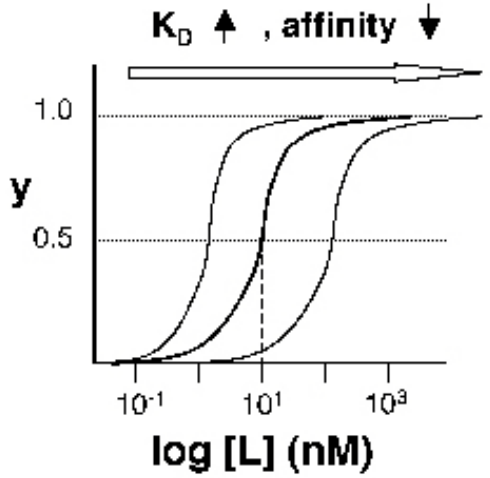
Actual binding curves are quite complicated:
Some discrepancies between ideal and actual conditions
Due to irreversible binding & artifactual binding sites

How to quantify the specific binding of a ligand?

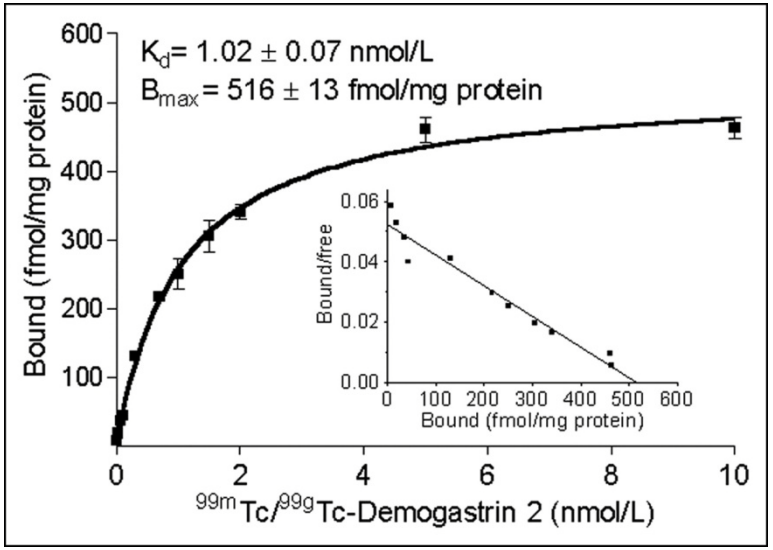
Kd: dissociation constant (binding affinity)

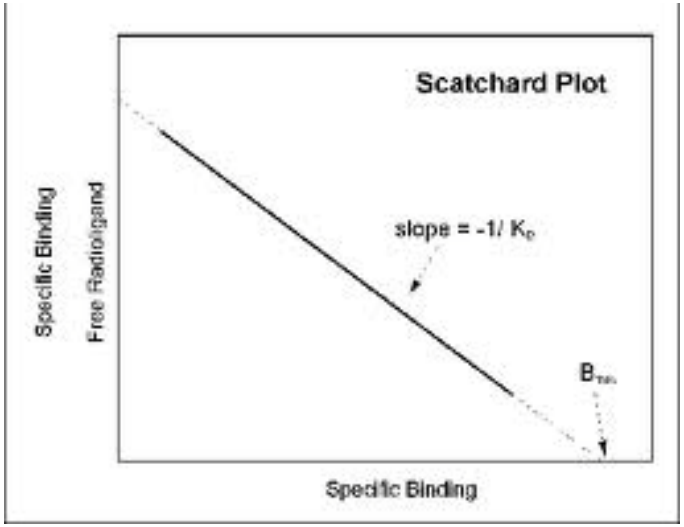
Bmax: total amount of binding



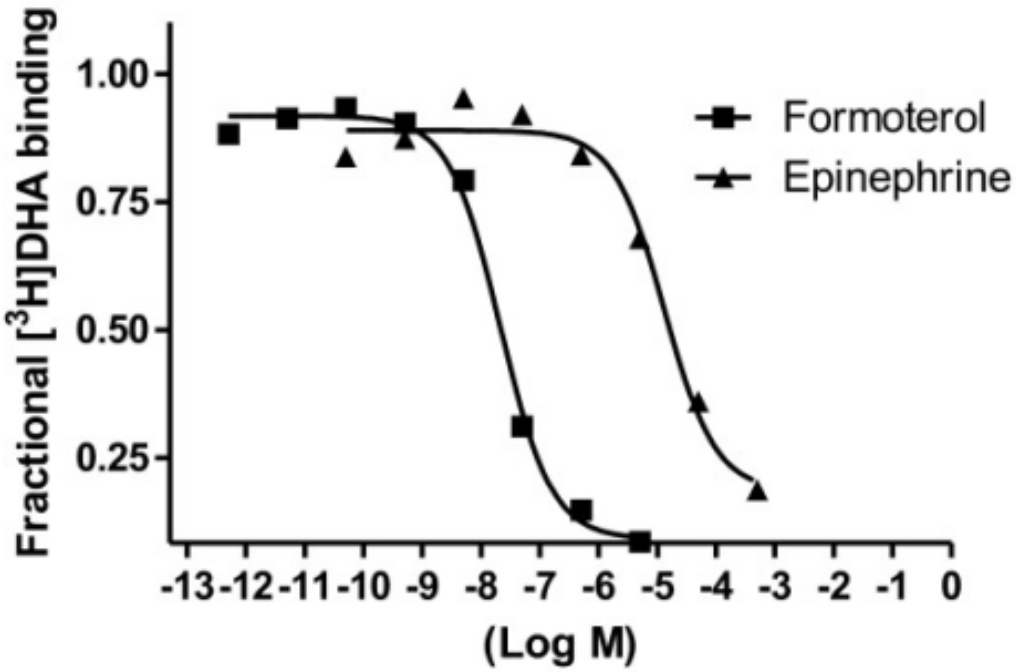


Transformed to Scatchard plot





Competition curve



Affinity competition curves for adrenergic ligands. Binding experiments were perfor med on crude material from cell-free reactions as described in methods using [3H] DHA and the indicated unlabelled competitors. To further characterize the cell-free expressed receptor, affinity competition experiments were carried out. The natural a ntagonist epinephrine and the high-affinity synthetic agonist formoterol were used

Drug potency & efficacy

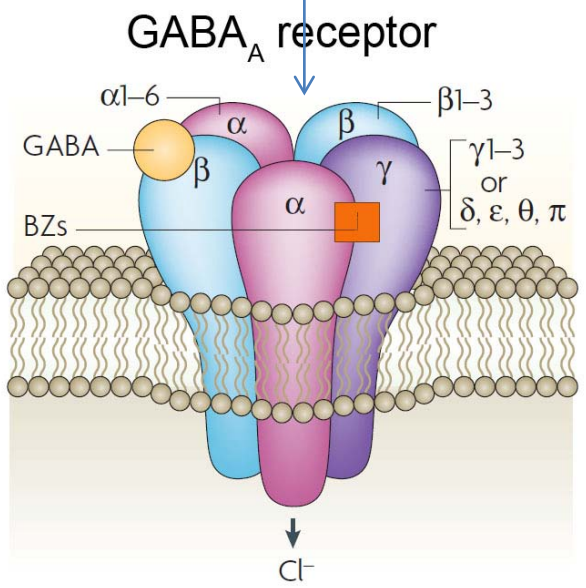
Potency (affinity, Kd): the strength of the binding
the physical relationship between drug and receptor
Efficacy: biologic effect

Drugs can differ dramatically with respect to their potency and efficacy

Complex nature of ligand-receptor interactions

Barbiturates
(noncompetitive agonist)

Muscimol (agonist)
Bicuculline (antagonist)
Competitive with GABA



Jacob et al., Nature Reviews Neuroscience, 2008

This site lacks endogenous ligands

Benzodiazepines (diazepam): agonist enhancing GABA binding

Flumazenil (antagonist): no effect but used for treating diazepam overdose

Beta-carboline (inverse agonist): intensify anxiety

Dose-dependent drug response