Lecture Contents -- Unit 2

- **Receptors, Ligands, and Drug Action**
  - **What is a receptor?**
  - **Ligand actions on receptors**
  - **Mechanisms of signal transduction**
  - **Neurotransmitters and their receptors**
  - **Other types of receptors**

Receptors: Some Definitions

- *Receptor:*
  An integral membrane protein (or protein complex) that can undergo conformational change upon ligand binding
- *Ligand:*
  Small molecule or peptide that can interact with a specific site of a receptor

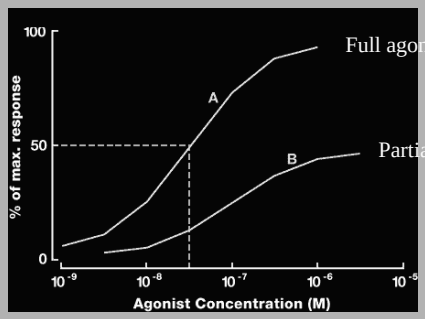
Ligand Actions at Receptors

- AGONISM**: positive action**
- ANTAGONISM**: prevention of positive action by displacement of agonist**
- PARTIAL AGONISM**: positive action, less pronounced than full agonist**
- INVERSE AGONISM**: opposite action relative to agonist**

Ligand-Receptor Affinity Measures

- **Affinity and potency of a particular ligand to its binding site can be expressed as K_m and pK values**
- **Parameter-free and practical (but model-dependent) measure: EC_{50} (= ligand concentration at which half-maximal effect of full agonist is achieved; IC_{50} for antagonists)**
- **Displacement efficacy vs. labeled standard high-affinity ligand**

In vitro concentration-response curves

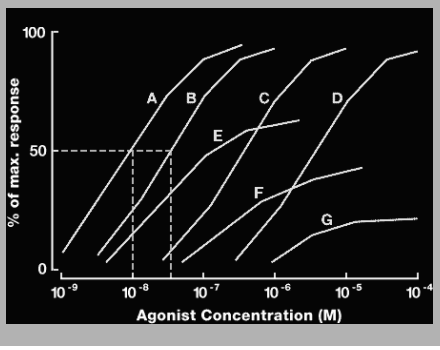


Full agonist

Partial agonist

http://www.glaxowellcome.co.uk/science/phguide

In vitro concentration-response curves

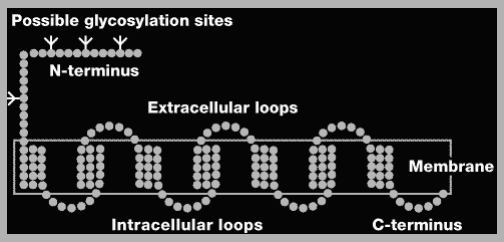


A = agonist alone

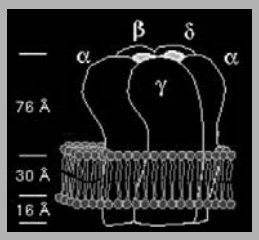
B,C,D = competive antagonist at incr. concentrations

E,F,G = non-comp. antagonist at incr. concentrations

Receptors are Transmembrane Proteins

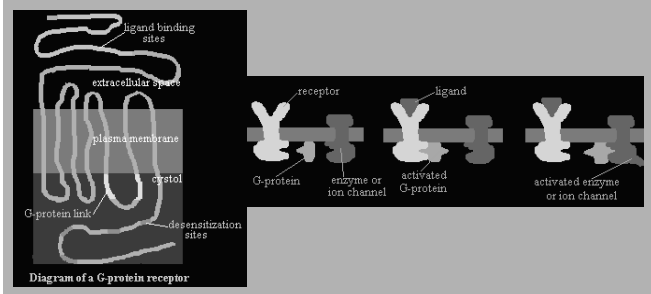


Receptors have Multiple Subunits

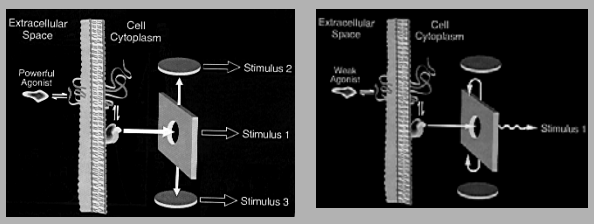


Human neuronal nicotinic acetylcholine receptor

Receptors Can Be Allosterically Activated



Receptor States And Ligands



Source: Pharmaceutical News

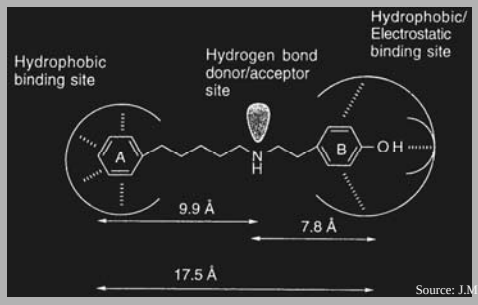
Receptors and Enzymes

	RECEPTOR	ENZYME
Binds small molecules in a non-covalent fashion	Yes	Yes
Ligand specificity	Yes	Yes
Allosteric modulation by ligands	Yes	Yes
Integral membrane protein	Yes	Some
Catalyzes chemical reaction or epimerization	No	Yes
Transmits signals between cellular compartments	Yes	No

„Modified Receptor Theory“ (Stephenson)

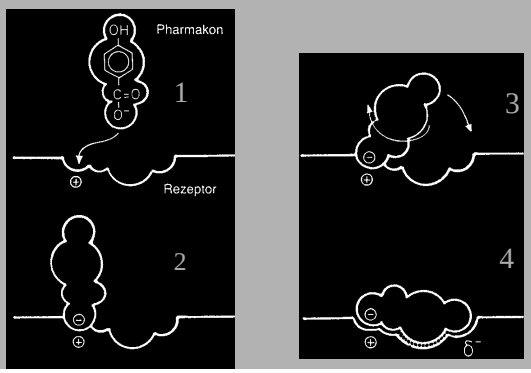
- **Ligand-bound receptor can adopt an inactive and an active state**
- **Action of agonists and partial agonists can be expressed in terms of two separable quantities:**
  - **“Efficacy” (determined by ligand affinity)**
  - **“Occupancy”**

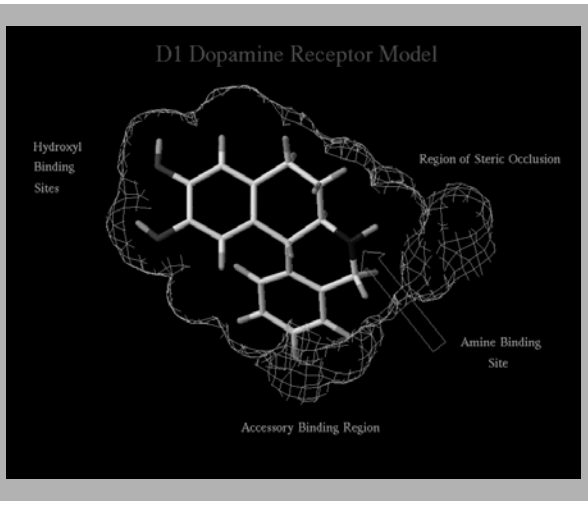
Receptor-Ligand Interaction Concepts



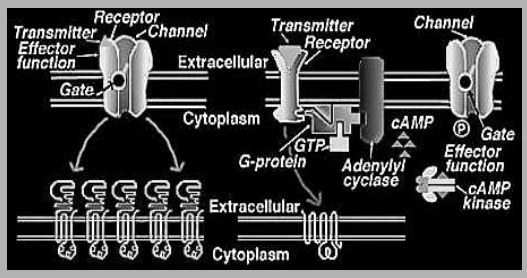
Source: J.Med.Chem.

Sequential Ligand Binding And Re-Orientation





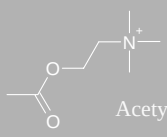
Ionotropic and Metabotropic Receptors



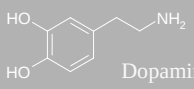
Neurotransmitters And Signal Transduction: Nobel Prizes for Medicine 1970

- **<u>V. Euler</u> (Karolinska Institutet, Stockholm): Noradrenaline is the signaling compound in the symphatetic neuronal system**
- **<u>B. Katz</u> (Gower Street College, London): Cholinergic signal transduction at the neuromuscular junction**

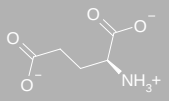
Some Major Neurotransmitters



Acetylcholine

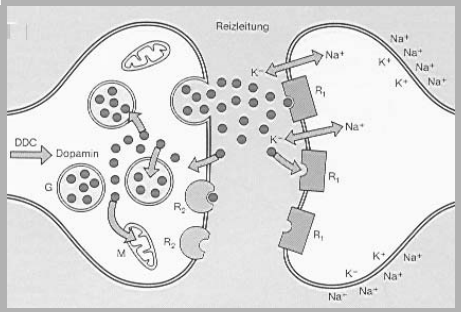


Dopamine

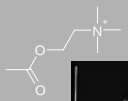


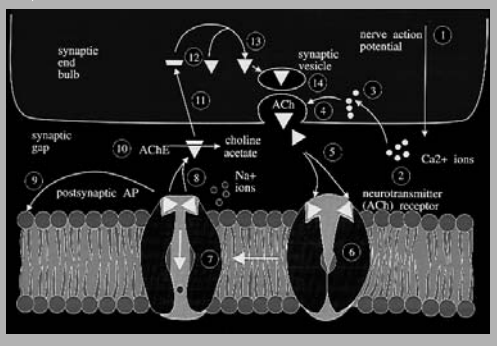
Glutamate

Neurotransmitters, Receptors, and Synapses: Dopaminergic

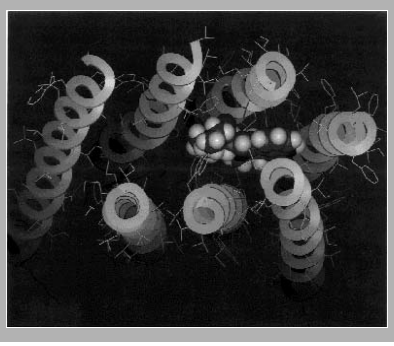


Neurotransmitters, Receptors, and Synapses: Cholinergic



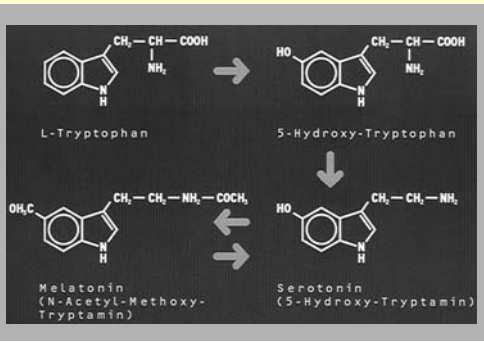


Rececptors In Addiction



LSD bound to serotonin receptor

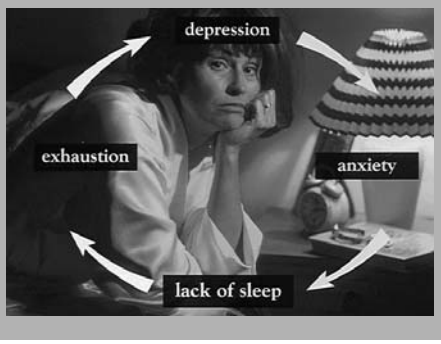
Serotonin: „The Neurotransmitter of the 90ies“



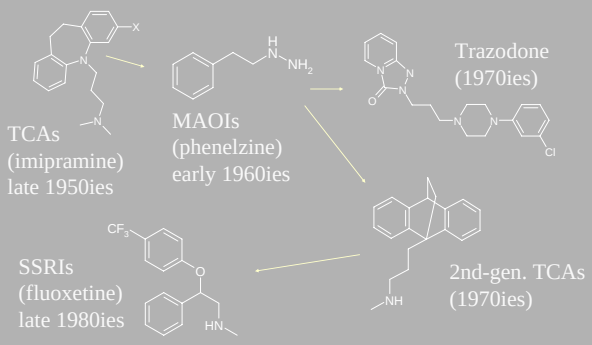
Depressive Illness: A Severe Psychiatric Condition

- **Common (occurs in 10% of men and 25% of women over lifetime)**
- **Disabling**
- **Life-threatening (10% commit suicide)**
- **Relapse-prone**
- **Changes brain biochemistry**
- **Responds to serotonergic drugs**

The Vicious Cycle Of Depression

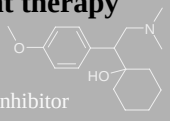


Pharmacotherapy Of Depression



Anxiety And Panic: The Twin Cousins Of Depression

- **Anxiety syndromes are extremely common**
- **Panic disorder with or w/o agoraphobia interferes severely with normal life**
- **Responds to antidepressant therapy**



Venlafaxine,
a selective serotonin reuptake inhibitor

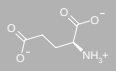
Serotonin Receptor Responses

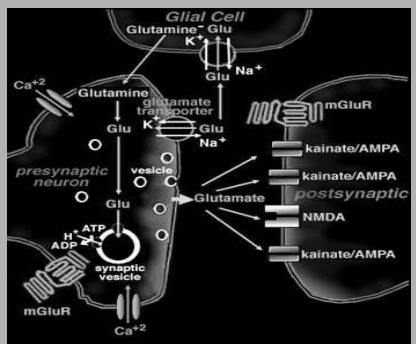
5-HT1 (A-F)	**5-HT2 (A–C)**	**5-HT3**
Cardiovascular	Vasoconstriction	Cardiovascular
Hyperphagia	Sexual effects	Nausea, emesis
Antidepressant	Muscle contraction	Anxiolytic
Sleep / sedation	Hallucinogenic	Pain
Migraine	Antipsychotic	Antipsychotic
Neuroprotection	Behavior	Migraine

Antidepressant Receptor Interaction Profiles

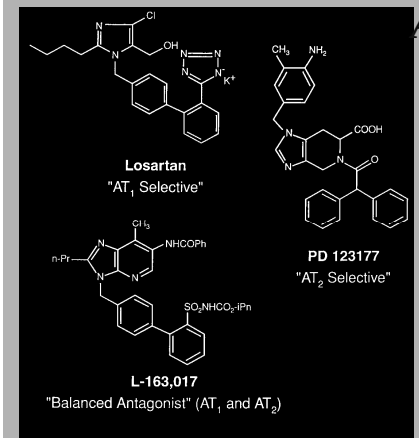
	NA	5-HT1	5-HT2	5-HT3
TCAs	+	+	+	+
Mianserin	+	+/-	-	-
SSRIs	+/-	+	+	+
NaSSAs	++	+	-	-

Glutamate: The Major Excitatory Neurotransmitter





Angiotensin Receptor Antagonists



Examples for receptor subtype selectivity in hypertension treatment