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9.98 Neuropharmacology
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Neuropharmacology:

The study of drugs specifically employed to affect the nervous system

Several drugs used for the treatment of extra-neural pathology may have an effect on the Nervous system

The effects of a drug can be considered at different levels:

- Molecular
- Cellular
- Behavioral

As the complexity of the system increases it becomes more difficult to predict the effects of a drug

Drug action:

molecular changes produced by a drug when it binds its target

There are two distinct aspects of drug action:

- Potency (the affinity of the drug for its receptor)
- Efficacy: the biological effects exerted on the target

How does a drug reach the brain?

Route of administration: Oral, Intravenous, Intramuscular, Subcutaneous, Inhalation, topical, Epidural.

Once in the body the drug binds to inactive sites that retain the drug and release it over time, this prolongs the action of a drug. Also, the amount of these proteins varies by individuals

The affinity of different drugs for these sites can explain some interactions between drugs

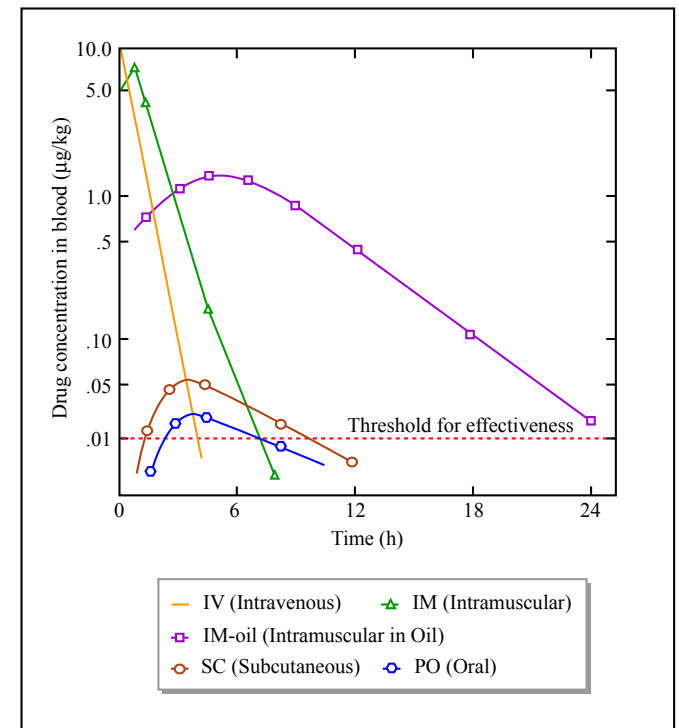


Figure by MIT OpenCourseWare.

This means that a drug stays in the blood for some time after administration
Before reaching the CNS, where it has to cross the Blood Brain Barrier

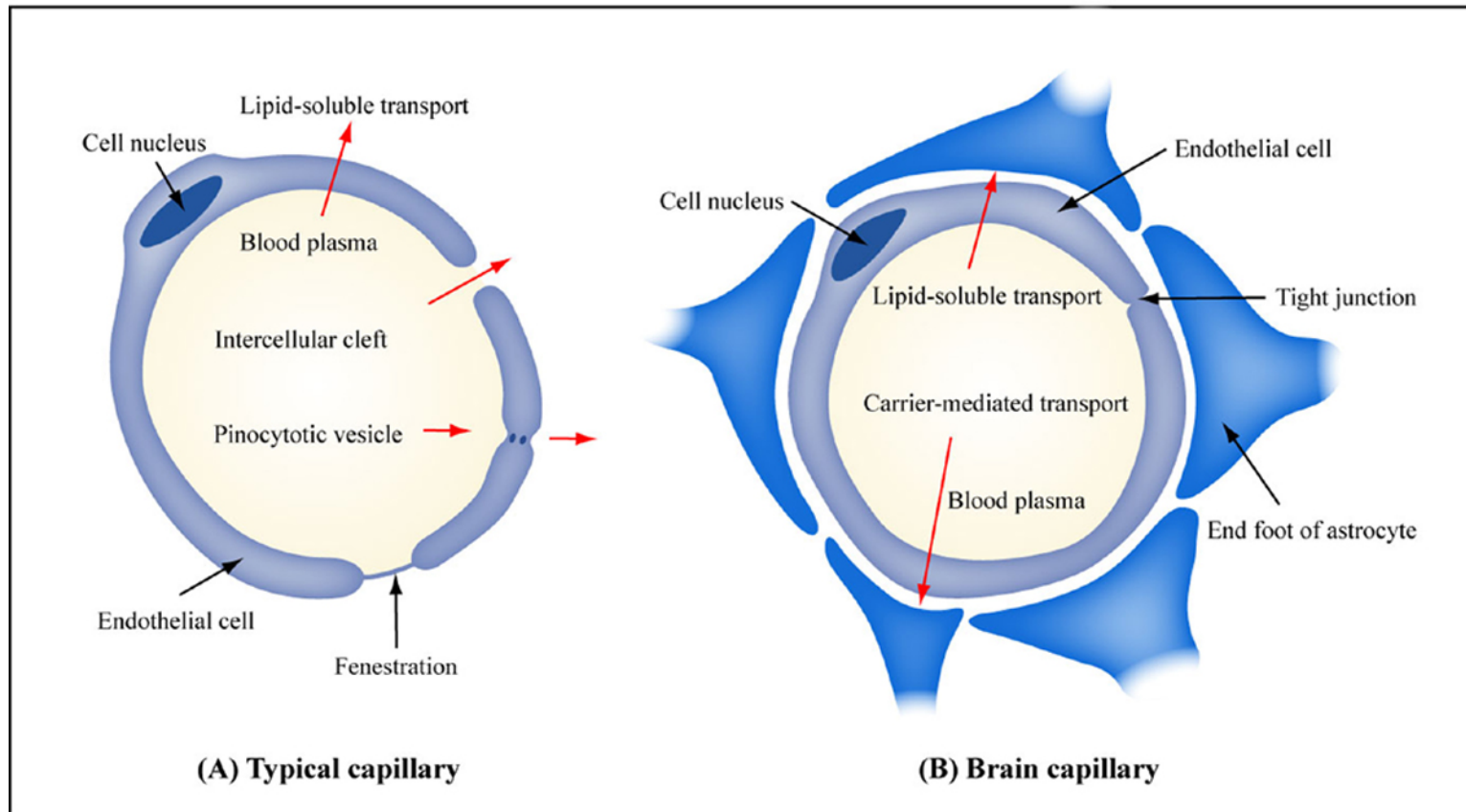


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The BBB barrier prevents that all the substances reach the brain
Also the placental barrier has to be taken into account.

Once the drug reaches the brain it can go through the cell membrane or
binds to a receptor on the cell surface

Drugs can be agonists or antagonists:

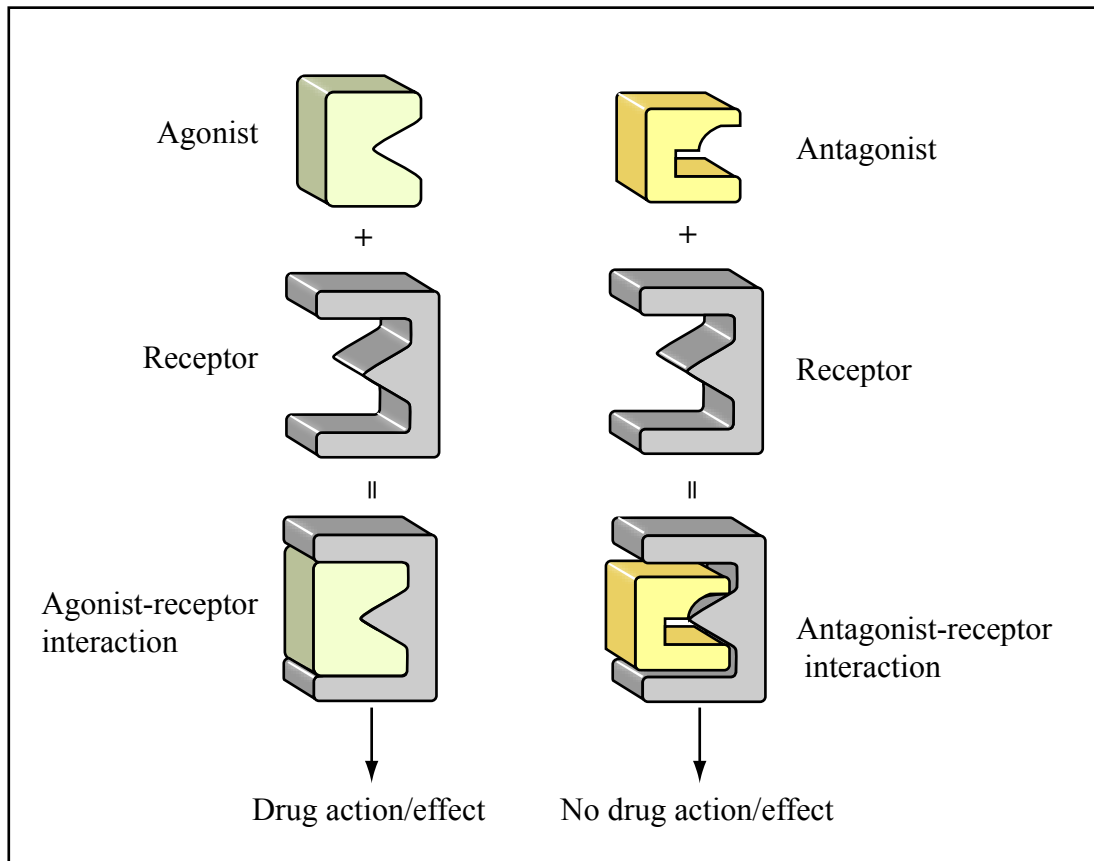


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Co-agonists

Competitive antagonists

Non-competitive antagonists

How do we measure the effects of a drug?

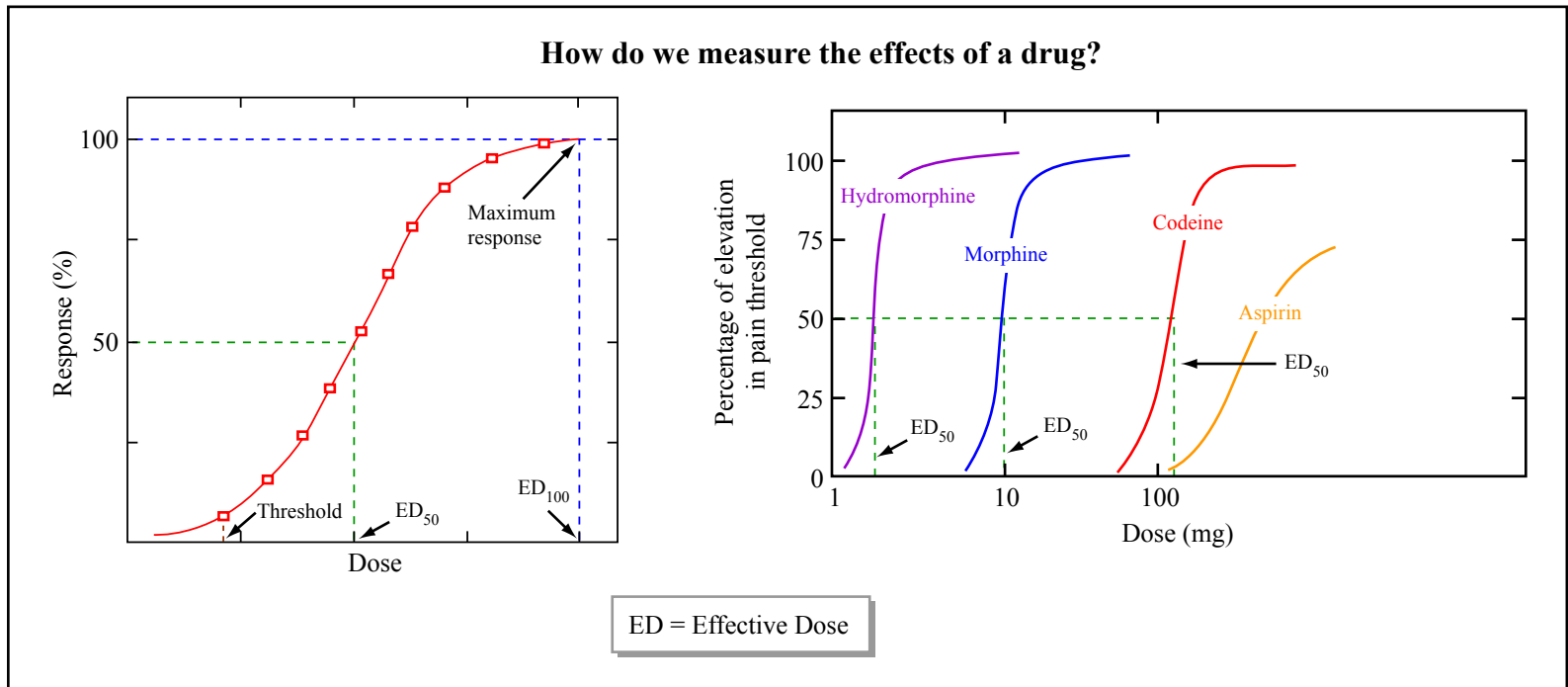


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...with the dosage-response curve (ED), which describes the amount of biologics or behavioral effect (response) for a given drug concentration (dose)

Dosage-response curves of different analgesics the first three have identical efficacy, even if at different dosage. The fourth is less effective

Drug effects

- Therapeutic effects
- Side effects

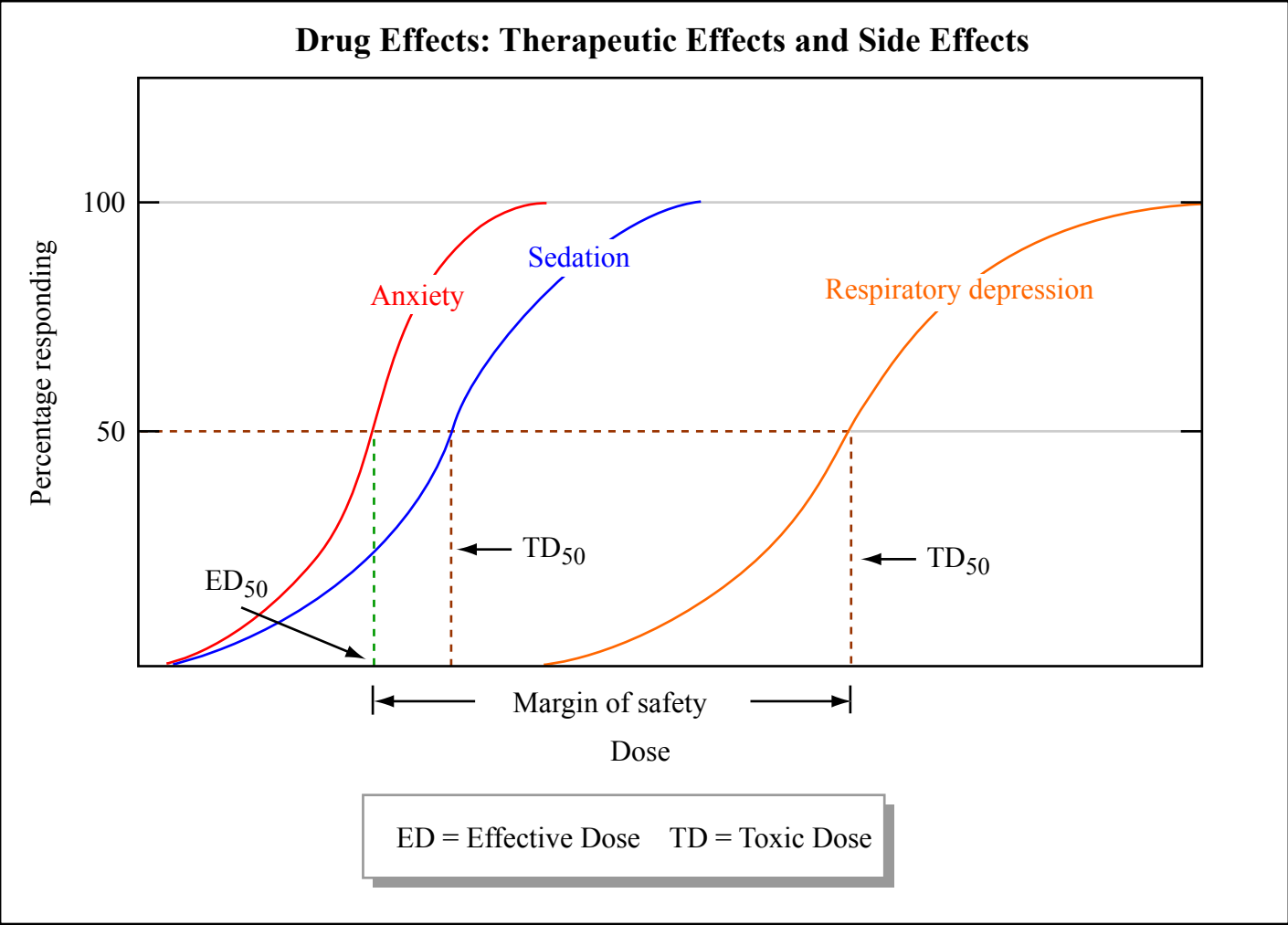


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Interaction between drugs. 1

Once in the body a drug is metabolized and eliminated, plus in the blood, the drug binds to non reactive substances such as albumin, that 'buffer' their action

One of the possible causes of interference is through the interaction of a drug with some of these molecules/enzymes.

Two drugs may act in different manners but having competitive effects (i.e.: on heart rate) On have ADDITIVE EFFECTS, or showing POTENTIATION (when the combination of two drugs produces effects that are greater than the sum of their individual effects).

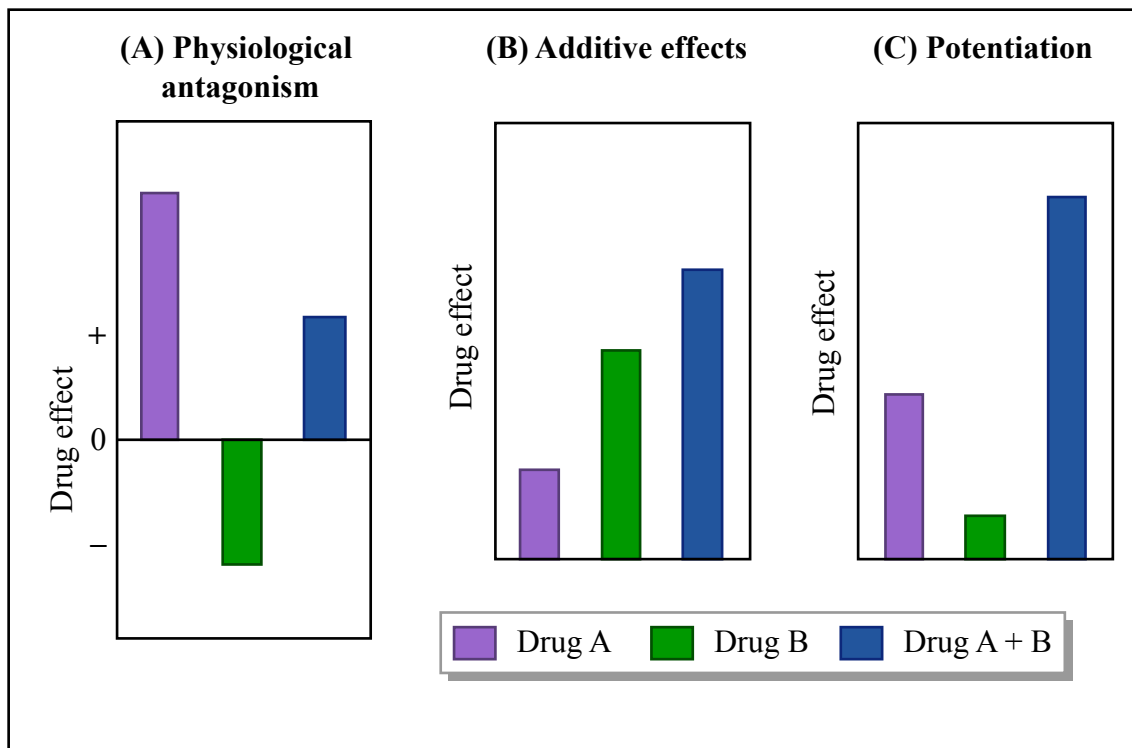


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Interaction between drugs. 2

Repeated use of a drug may cause an altered production of metabolic enzymes involved in the catabolism of several drugs. Example: some anti-seizure drugs interfere with the metabolism of oral contraceptives. A similar effect is produced by cigarette smoke

Drug competition: when drugs share the metabolic system. Es: alcohol increases the metabolism of Valium increasing its effects.

Metabolic enzymes are different at different ages and different gender therefore producing different effects

The response to a drug can change over time

TOLERANCE: a diminished response to drug administration after repeated exposures of that drug (metabolism or compensatory changes in the nerve cell)

SENSITIZATION (reverse tolerance), when repeated drug administration causes an enhancement of the drug effects

Up- or down-regulation of the receptors (1/2 weeks) reflect compensatory changes

Basic properties of the nerve cells:

- Ability to conduct electric signals
- Specific intercellular connections with other nervous cells or with other tissues

Drugs can affect either one of these properties

Also, glial cells in the brain are important for modulating neuronal function

Basic elements of biophysics

Neurons transmit electrical signals. At the cell membrane there is a different Distribution of ions that causes a resting potential of -70mV . This situation is Maintained through ATP-pumps that maintain Na^+ and Cl^- ions concentrated outside the cell and K^+ localized inside.

Image removed due to copyright restriction. Figure 2.10 in Meyer, and Quenzer, *Psychopharmacology*, 2004.

The ions can go across the membrane through channels. The ion channels are Open depending on voltage, ligand, or biochemical modification (i.e. phosphorylation)

Image removed due to copyright restriction. Fig 2.7 in Meyer and Quenzer, *Psychopharmacology*, 2004.

Local changes in ion concentration induce local potentials, and when these events sum up and a threshold is reached, a great number of voltage-gated channels is opened allowing a massive depolarization known as action potential.

After the propagation of the signals the channels close (refractory period) until the ion distribution is restored.

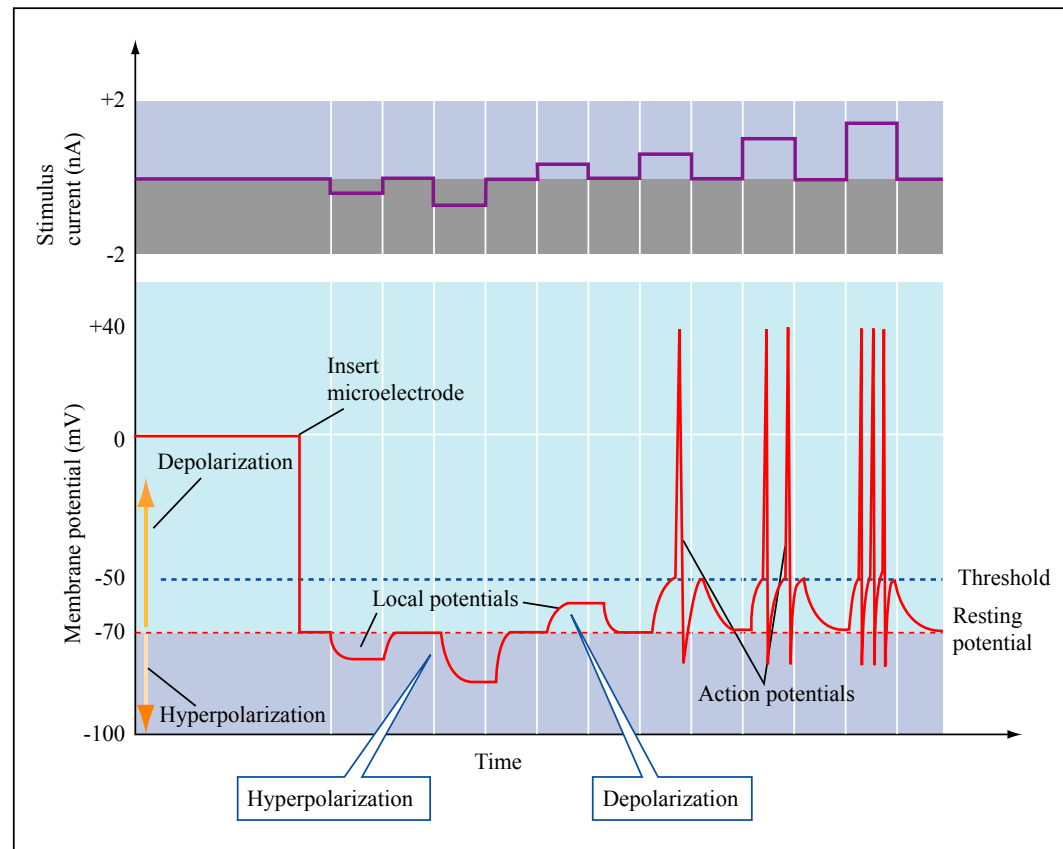


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Lidocaine, a topic anesthetic, blocks the Na^+ channels therefore blocking the transmission of pain

Phenytoin (Dilantin) is used to prevent epilepsy. It binds to Na^+ channels during the refractory period preventing their opening, therefore preventing the spreading of electrical activity

Modulation of synaptic transmission

It is based on the interaction between a neurotransmitter, released by the presynaptic terminal, and its receptor on the postsynaptic receptor

Regulated from molecules that peptides that affect neuroactivity, even without being transmitters

Many neurotransmitter have more than one receptor

Receptors:

- Ionotropic
- Metabotropic

TABLE 3.1 Major Categories of Neurotransmitters^a

Classical neurotransmitters	Non-classical neurotransmitters
Amino acids	Neuropeptides
Glutamate	Endorphins and enkephalins
γ-aminobutyric acid (GABA)	Corticotropin-releasing factor (CRF)
Glycine	Many others
Monoamines	Lipids
Dopamine (DA)	Anandamide
Norepinephrine (NE)	Gases
Serotonin (5-HT)	Nitric oxide (NO)
Acetylcholine	

^aIt should be noted that this is only a small sample of the more than 100 substances known or suspected to be neurotransmitters in the brain.

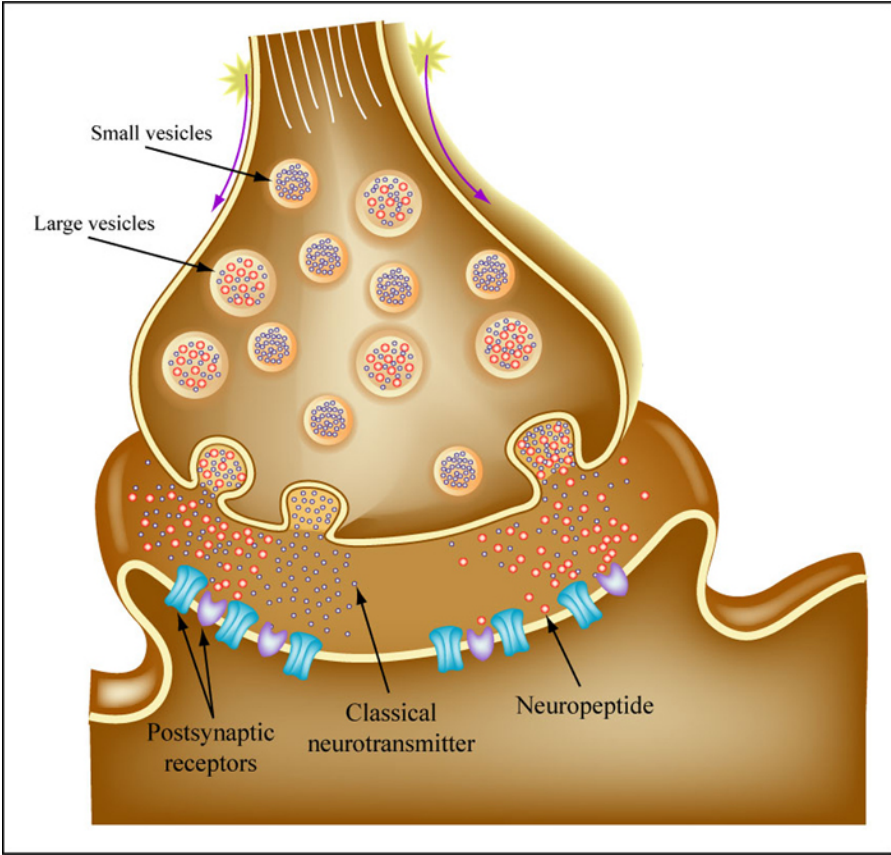


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Scheme of Neurotransmitter Release

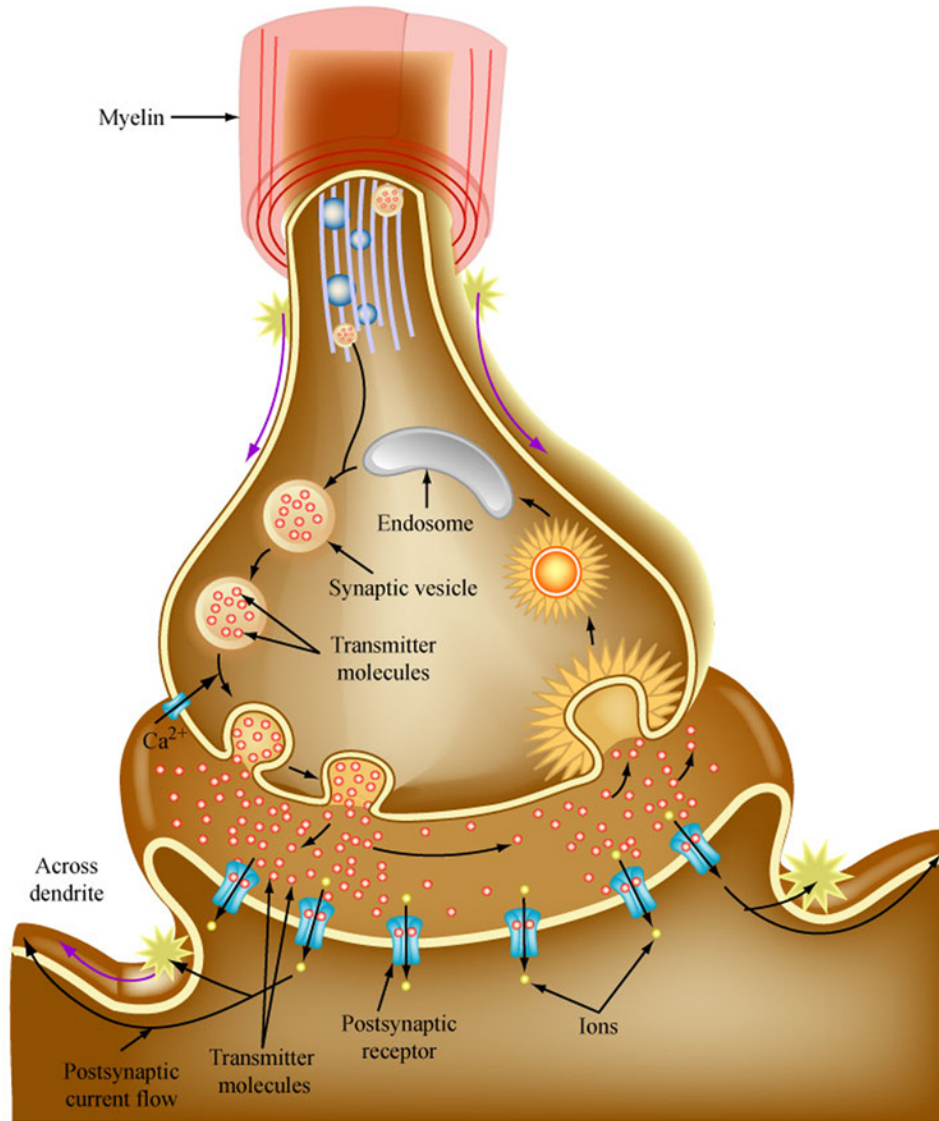


Figure by MIT OpenCourseWare.

A particular case of neurotransmitter is represented by NO: Nitric Oxide. It is a gas Therefore it is not stored in vesicles and it can cross the membranes. It is also Produced by the post synaptic element and it can act as a retrograde signal. The only way to modulate its availability is by modulating its synthesis operated By the enzyme Nitric Oxide Synthase (NOS). NO action results in the activation of an enzyme that produce cGMP (a second Messenger). Blocking NOS prevents the tolerance and the dependence induced by drug administration. This may have an effect on the tolerance for drugs used for the treatment of chronic pain.

Another effect of cGMP activation is to relax the smooth muscle that surround the Blood vessels therefore increasing arteries dilatation; cGMP degradation is catalyzed By the enzyme cGMP phosphodiesterase. If this enzyme is blocked the effects of NO are potentiated facilitating arteries dilatation. Is this the mechanism used by the drug sildenafil (known commercially as VIAGRA)

Ionotropic receptors comprise multiple protein subunits that form an intrinsic ion Channel. They mediate fast excitatory and inhibitory neurotransmission

Metabotropic receptors are constituted by one single unit and their activation stimulate a second messenger system that eventually leads to activation of ion channels and protein kinases. Their action is slower but long-lasting

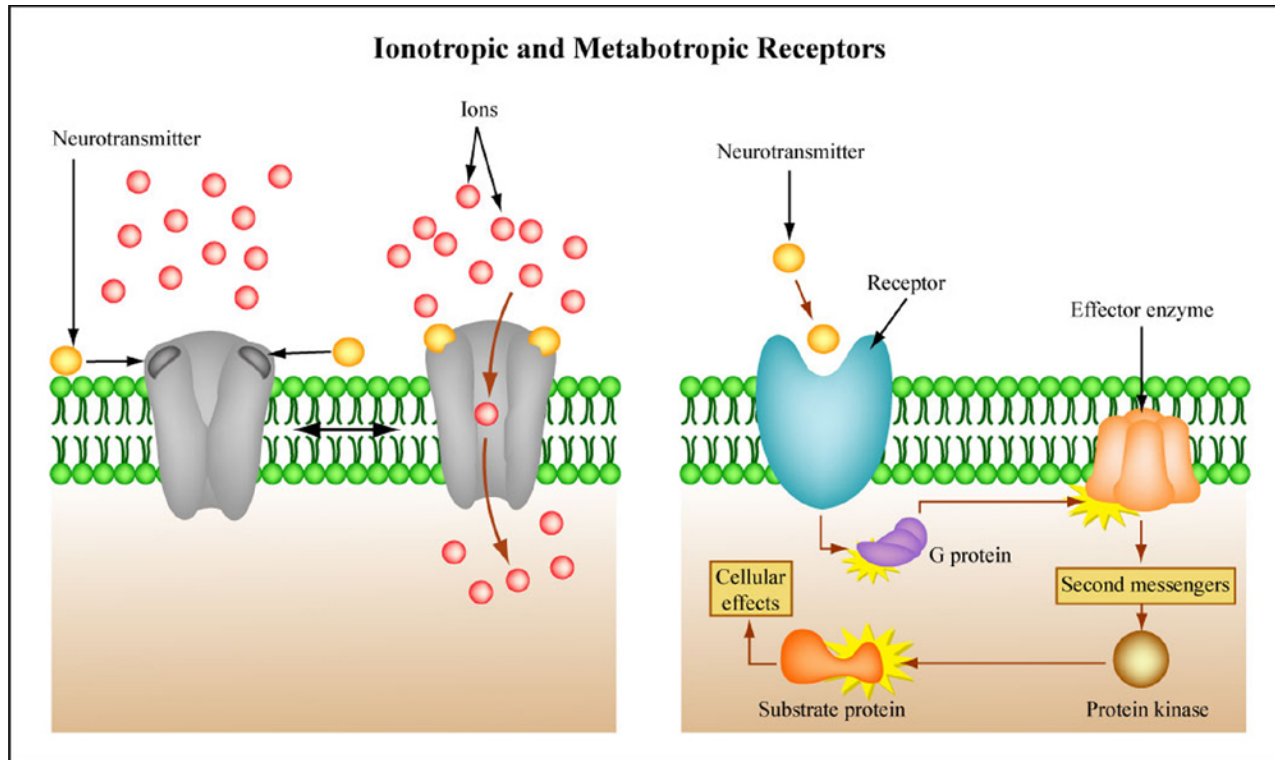


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TABLE 3.2 Comparison of Ionotropic and Metabotropic Receptors

Characteristics	Ionotropic receptors	Metabotropic receptors
Structure	4 or 5 subunits that assemble in the cell membrane	1 subunit
Mechanism of action	Contain an intrinsic ion channel that opens in response to neurotransmitter or drug binding	Activate G proteins in response to neurotransmitter or drug binding
Coupled to second messengers?	No	Yes
Speed of action	Fast	Slower

Scheme of Synaptic Transmission

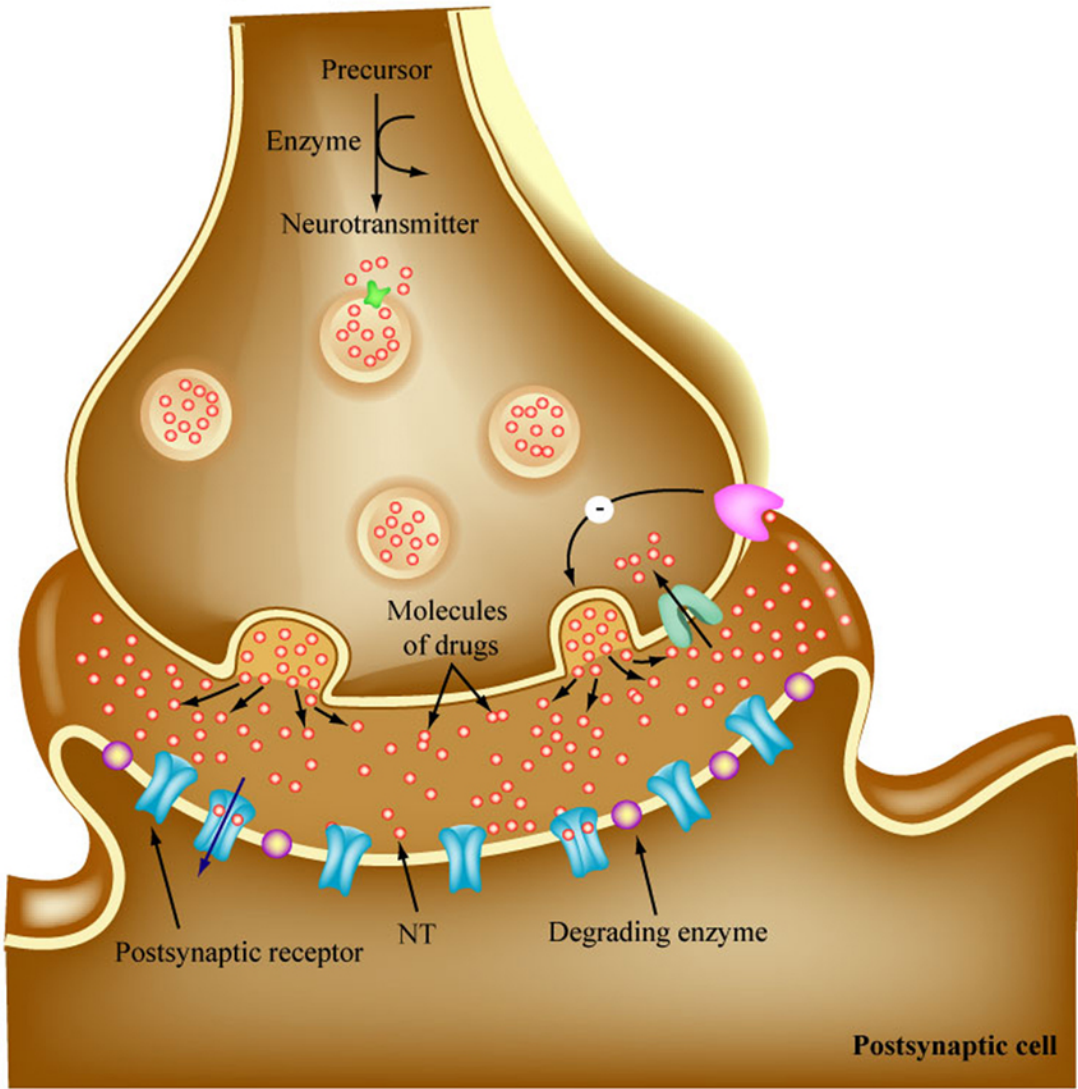
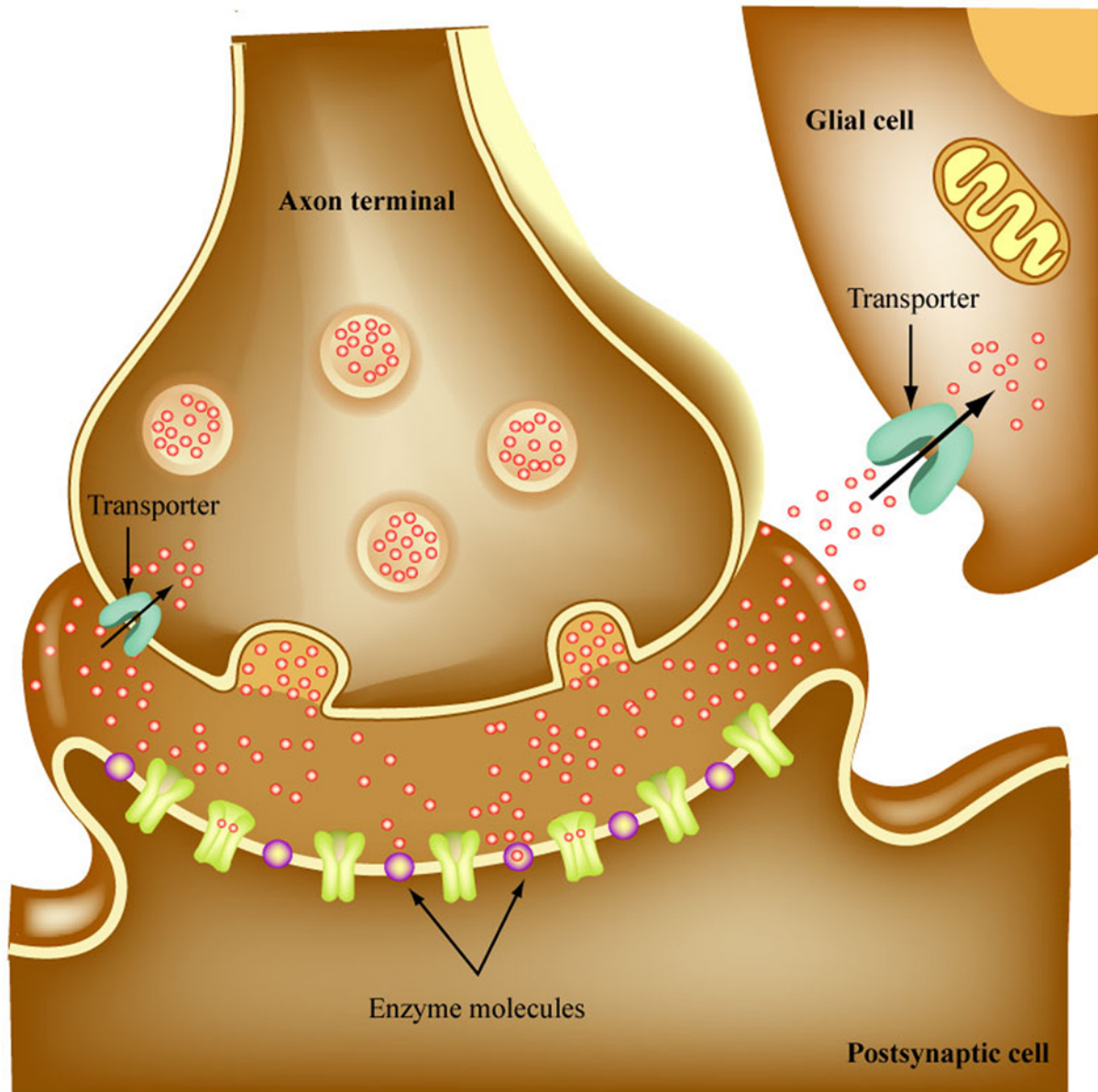


Figure by MIT OpenCourseWare.

Transporters are localized on Glia



Presynaptic modulation (the amount of transmitter released)

- Change in the firing frequency of the presynaptic neuron
- Change in the synthesis, storage, transport, release, reuptake, catabolism of a transmitter
i.e. L-DOPA (the precursor of DA) is given to patients with Parkinson's disease,
i.e.: drugs that block monoamine oxidase (MAO) that degrades serotonin (5-HT) are used to treat Depression, and so are drugs that prevent the re uptake of the neurotransmitter
- Direct effect on the release mechanism by changing the electric properties of the terminals or modulating specific molecules involved in the release process

Postsynaptic modulation

- Long term changes in the number of receptors (use of agonist or antagonist drugs)
- Change in the affinity of a ligand for a receptor
- Change in ionic conductance (2nd messenger)

Neurotransmitter system: glutamate

Glutamate mediates fast excitatory transmission and it is present in all the cells of nervous system

Image removed due to copyright restriction. Fig. 7.3 in Meyer and Quenzer, *Psychopharmacology*, 2004.

Glutamate is generated from glutamine (via glutaminase) and it is loaded into vesicles by VGLUTs, which are present only in glutamatergic cells. Once released in the synaptic cleft glutamate is removed by neuronal and glial transporters: Excitatory Amino Acid Transporters (EAATs). EAAT1/2 are present on astrocytes and are important for modulating the amount of extracellular glutamate. Excess of glutamate can be dangerous and even produce cell death

Abnormalities in EAATs lead to diseases: half of the cases of Amyotrophic Lateral Sclerosis (ALS) are caused by EAATs and cause degeneration of motor neurons.

Excitotoxicity hypothesis: excessive exposure to glutamate and related amino acids cause a prolonged depolarization of neurons that lead to their damage and death

Domoic acid is an excitatory amino acid made by some algae. It concentrates in crabs, Shellfish and fish. When wild life eat these sources they get intoxicated. This happened in 1961 in Capitola (CA) and inspired the movie “the birds”.

Image removed due to copyright restrictions.
Still photo from *The Birds* by Alfred Hitchcock.

Glutamate receptors are formed by different subunits that are targeted by different drugs

Image removed due to copyright restriction. Fig. 7.4 in Meyer and Quenzer, *Psychopharmacology*, 2004.

alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA)

N-methyl D-aspartate (NMDA)

NBQX (2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2,3-dione) is a blocker for AMPA and Kainate receptors but not for NMDA. Rodents treated with NBQX show sedation, poor coordination of movements and protection from chemically-induced seizures.

There are also metabotropic receptors

NMDA receptors have binding sites for glutamate and for other binders: Glycine and D-serine are co-agonists. They are necessary for the activation Of the receptor, but the limiting factor is glutamate.

There are also blockers: Mg^{++} blocks the receptor, but it leaves its site when the Membrane is depolarized

Images removed due to copyright restriction. Fig. 7.5 and fig. 7.6
in Meyer and Quenzer, *Psychopharmacology*, 2004.

So for the activation of NMDA receptors two events are necessary: glutamate and Membrane depolarization. Inside the channel there are three more bindings sites: For phencyclidine (PCP), ketamine and MK-801. These substances block the channel (non competitive antagonists)

GABA (Gamma-aminobutyric acid) and glycine are two inhibitory neurotransmitters.
Blockade of GABA transmission induces seizures.

GABA is synthesized from Glutamate by the enzyme Glutamic Acid Decarboxylase (GAD) Which is present only in inhibitory neurons. GABA synthesis can be blocked by the following drugs:

Allylglycine, thiosemicarbazide, 3-mercaptopropionic acid

Image removed due to copyright restriction. Fig. 7.13 in Meyer and Quenzer, *Psychopharmacology*, 2004.

Similarly to Glutamate, GABA is loaded into vesicles by VGAT, and it is removed from the synaptic cleft by transporters located on both neurones and glia: GAT-1, GAT-2, GAT-3. Tiagabine (GABITRIL), blocks specifically GAT-1, enhances GABAergic transmission and it is used in the treatment of epilepsy.

Another way to increase GABAergic transmission is to reduce the degradation of GABA by blocking the enzyme GABA aminotransferase (GABA-T). Vigabatrin (SABRIL) is an irreversible inhibitor of GABA-T and it is used in certain types of epilepsy.

Diazepam (VALIUM) is a synthetic product that increases GABA_A receptor function, however there are endogenous molecules that show a benzodiazepine-like activity: endozepines, which may play a role in anxiety. There is also an endogenous peptide that inhibits diazepam by binding to the diazepam binding site (DBI: diazepam binding inhibitor).

Benzodiazepines have a specific binding site: substances that bind to the site act as convulsants, because they decrease the GABA transmission.

There are two main type of GABA receptors: GABAA (ionotropic) and GABAB (metabotropic)
GABAA receptor consists of a channel for Cl⁻. Drugs that interact with GABA are:

Muscimol (agonist)

Bicuculline (antagonist)

Pentylentetrazol (antagonist)

Benzodiazepines*

Barbiturates*

Neurosteroids (agonists)

Ethanol (agonist)

Image removed due to copyright restriction. Fig. 7.14 in Meyer
and Quenzer, *Psychopharmacology*, 2004.

Baclofen (LIORESAL) is an agonist for GABAB receptors and it is used as a muscle relaxant and
Antispastic

* They activate the receptor together with GABA. There is no effect in absence of GABA