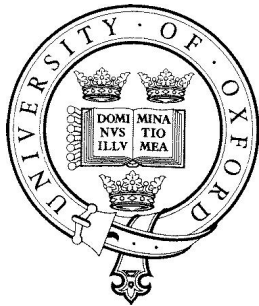


Synapses: Electro-Chemical Signalling and Decision Making

How Your Brain Works - Week 2



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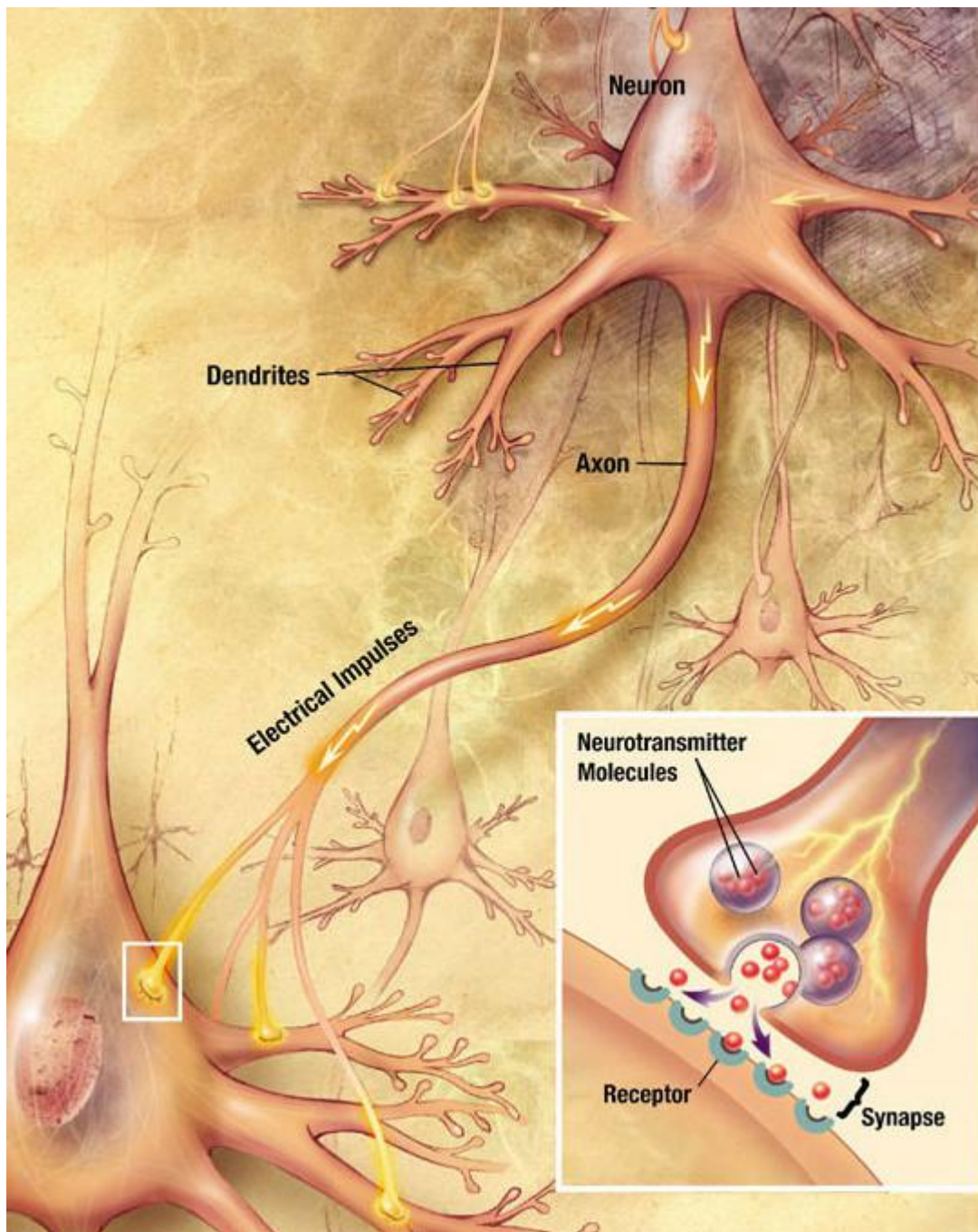
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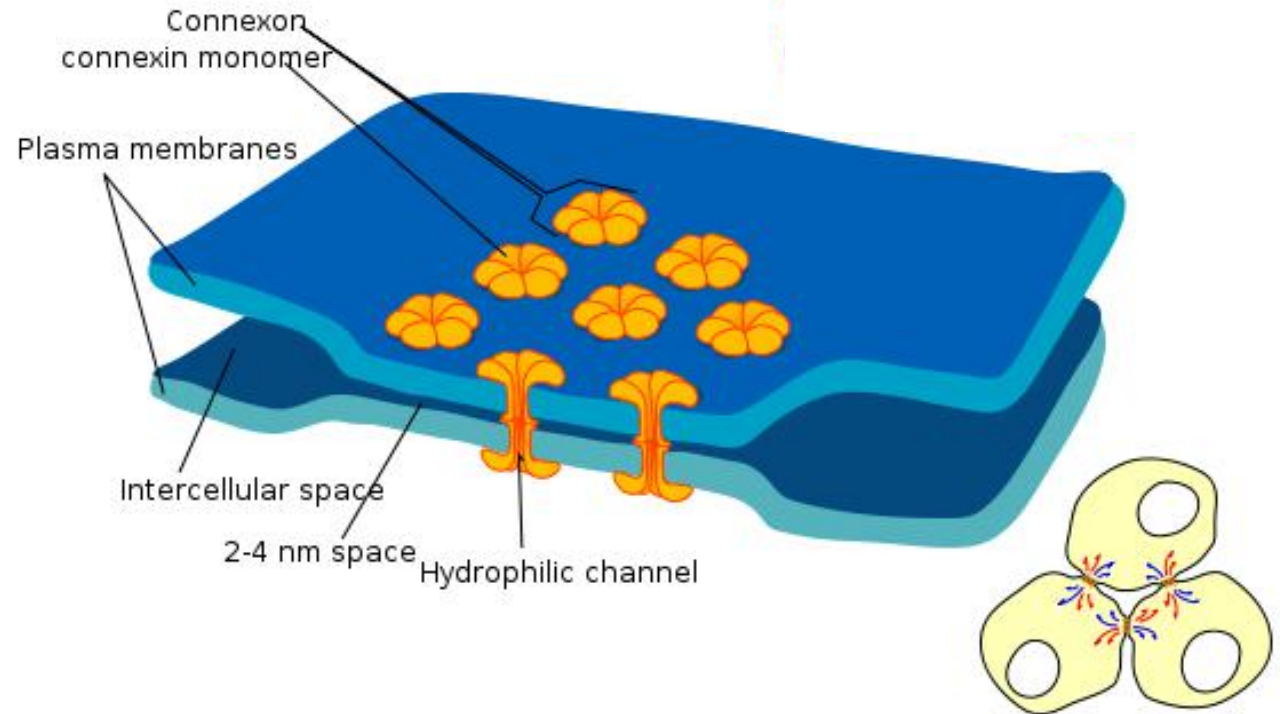
Let's recap from last lecture:

- Neurons carry an electrical potential (voltage) across their membranes.
- Opening and closing of ion channels changes the membrane potential. This can encode external stimuli as electrical signals.
- To send signals over large distances through their axons, neurons need to generate action potentials (nerve impulses or “spikes”), necessitating the creation of “spike codes” to represent the outside world inside our heads.

Getting
signals from
one neuron to
the next:
synapses



“Electrical Synapses” (Gap Junctions)



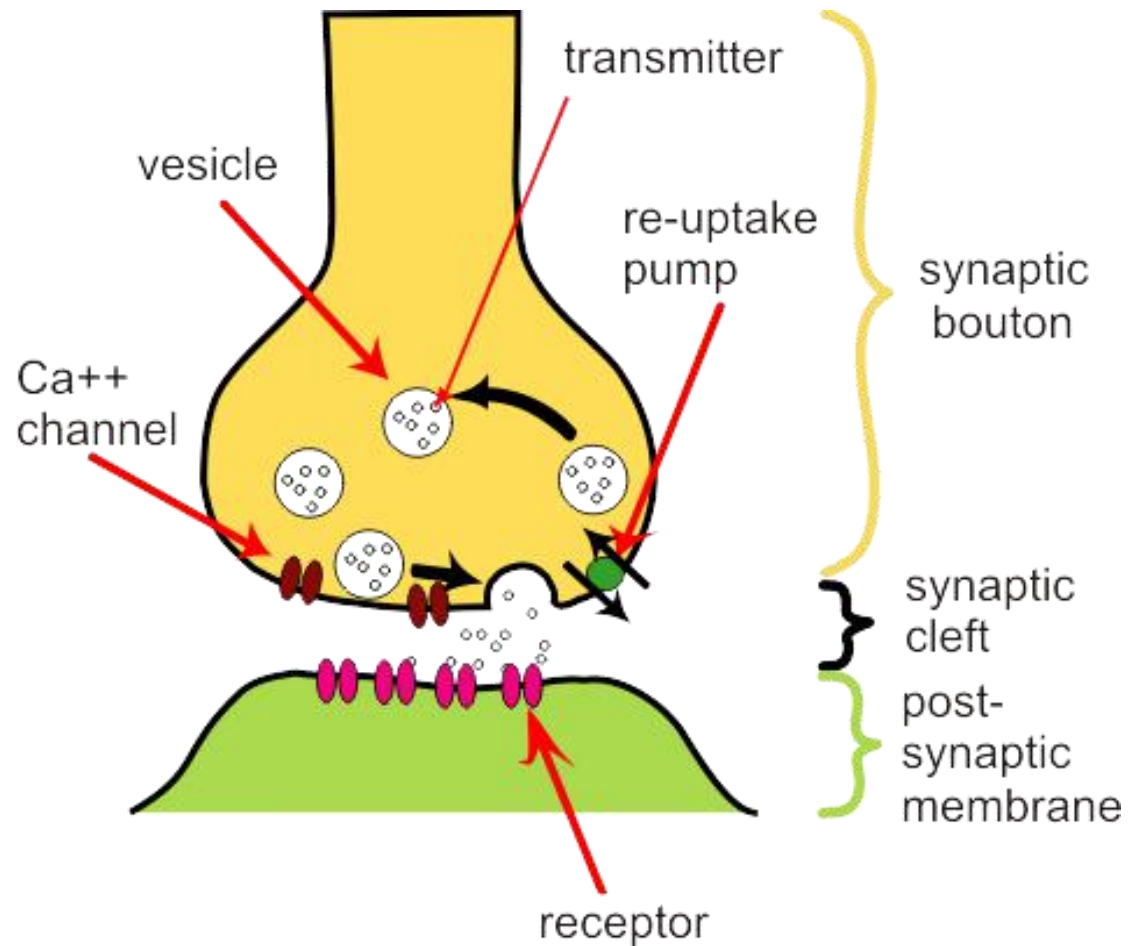
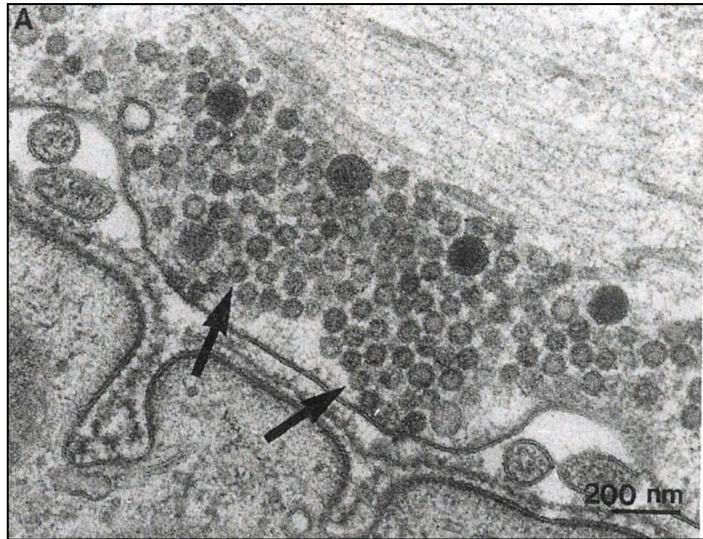
- Gap Junctions are thought to play a relatively minor role in the brain.
- They are quite simple: currents carried by ions simply flow through channels from one cell to another, but that is probably precisely why the brain does not seem to make much use of them. They are too simple!

The NMJ: a “Prototypical” Synapse

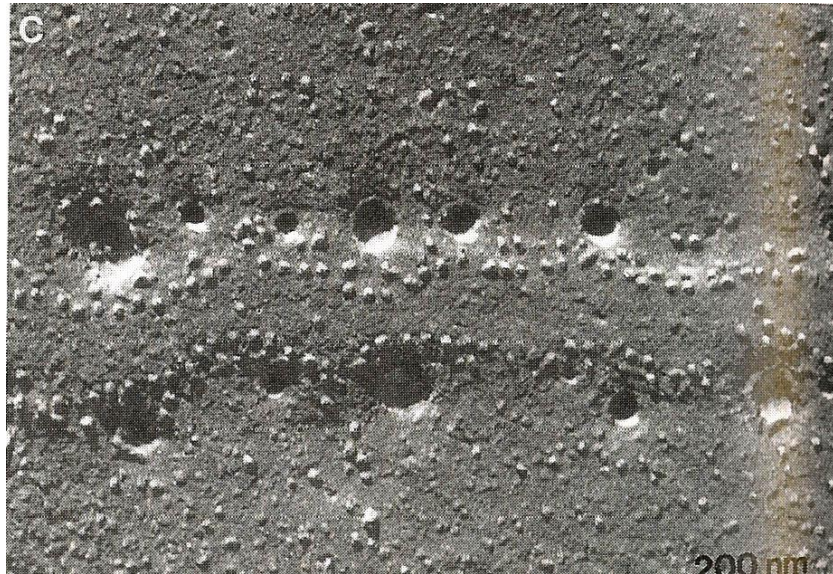
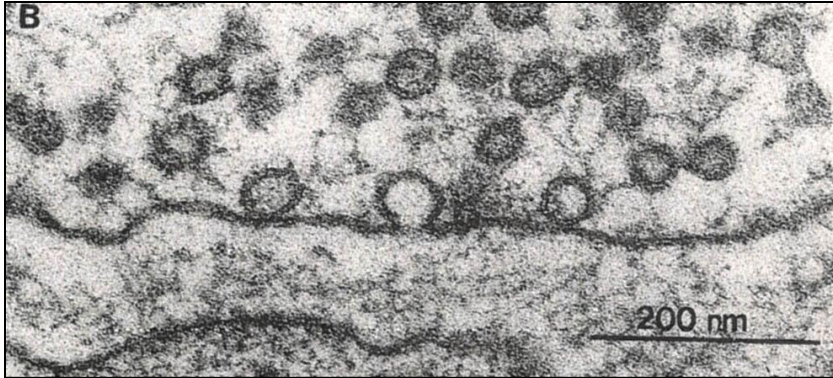
- The neuro-muscular junction (NMJ) is very large and easily accessible. It is therefore the first synapse to be studied in detail.
- The motorneuron axon forms a number of *presynaptic buttons* in the end-plate region of the muscle fibre.



Synapse Morphology



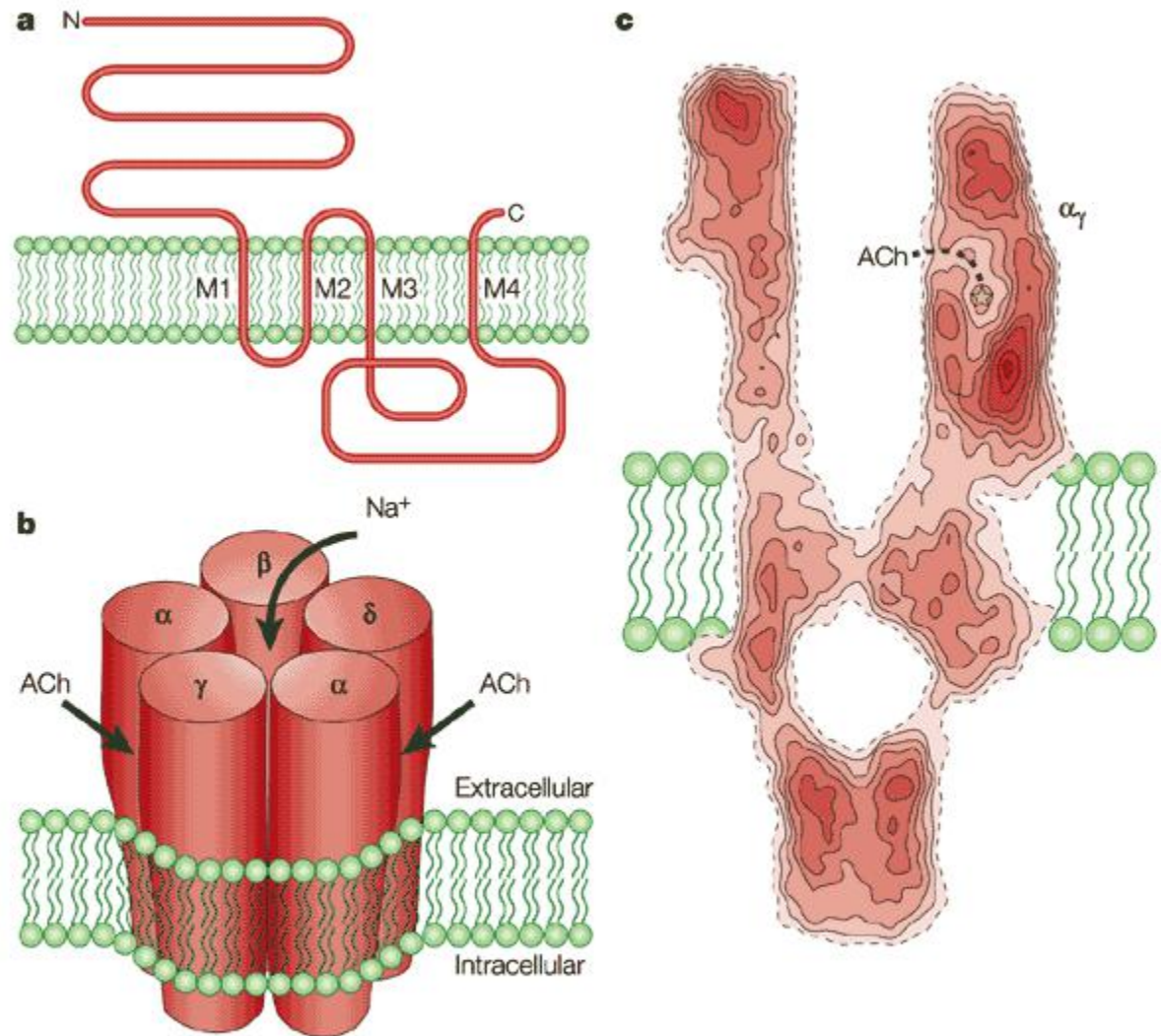
Neurotransmitter Release



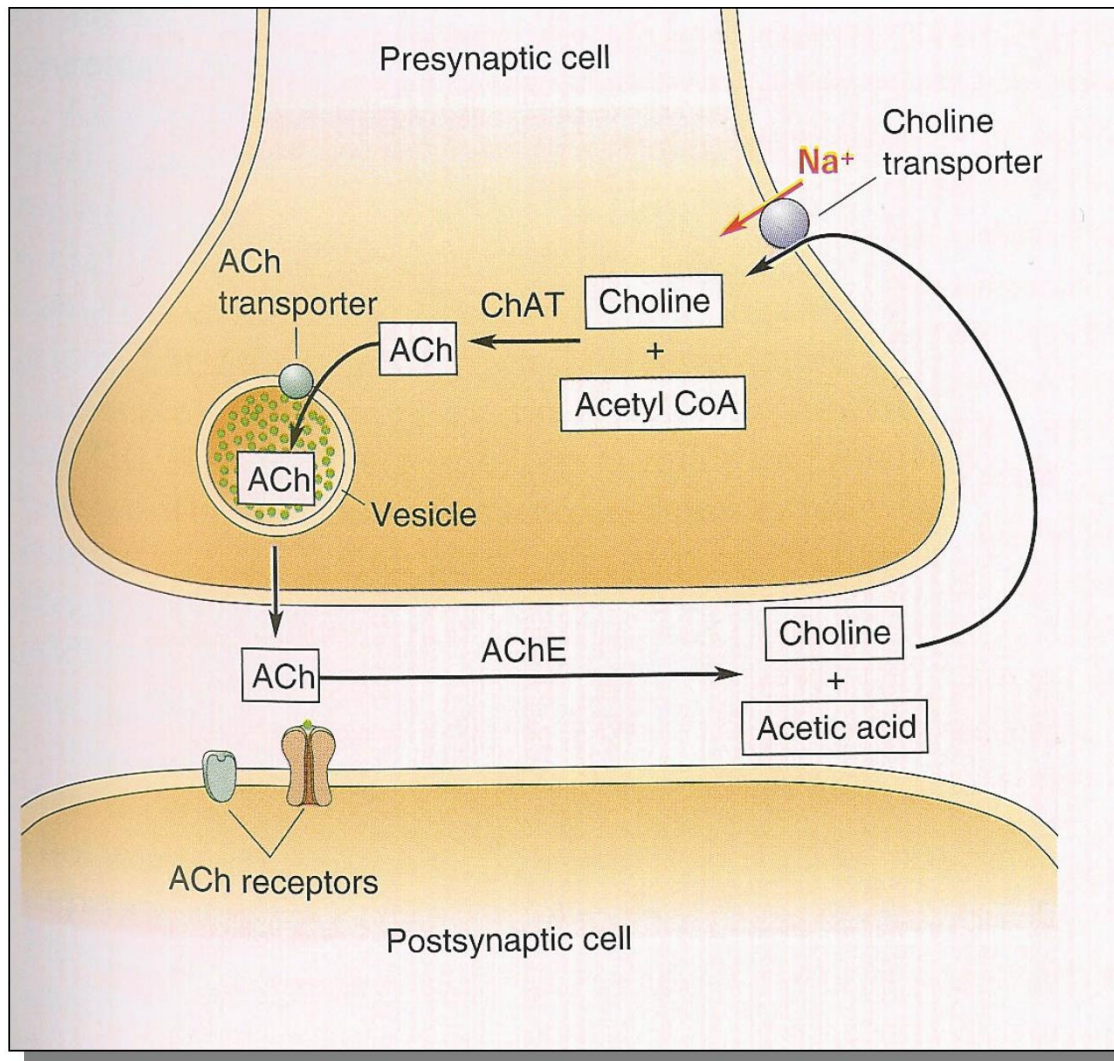
- Action potentials arriving at the presynaptic membrane open voltage gated Ca^{++} channels.
- This activates proteins that facilitate the fusion of vesicles with the cell membrane to make them release their contents into the synaptic cleft: **“exocytosis.”**
- Neurotransmitter released in this way diffuses through the cleft and binds to receptor proteins on the post-synaptic neuron.

The Acetyl-Choline Receptor (AChR)

- The **AChR** is a transmembrane protein
- It binds 2 ACh molecules
- ***The receptor is a gated ion channel***
- ACh binding causes a shape change that allows Na^+ and K^+ to pass through the channel



Terminating the Chemical Signal



- ACh does not remain bound to the AChR indefinitely.
- When it dissociates, it may be cleaved by **acetyl-cholinesterase (AChE)**, preventing binding to another AChR.
- The choline produced by ACh breakdown is taken back up into the presynaptic bouton and recycled.

Diversity of Neurotransmitters

- The brain uses a large variety of different transmitter substances. Dozens of transmitters have already been discovered, and more are likely to be added to the list.
- Although there are so many substances, some are used much less than others. By far the most commonly used transmitters in the brain appear to be **glutamate** and **GABA**.
- “**Dale’s principle**”: a neuron will typically release only one type of transmitter. However, although a given neuron typically releases only one type of transmitter, most neurons in the brain are receptive to a variety of different transmitters.

Chemical Transmitter Classes

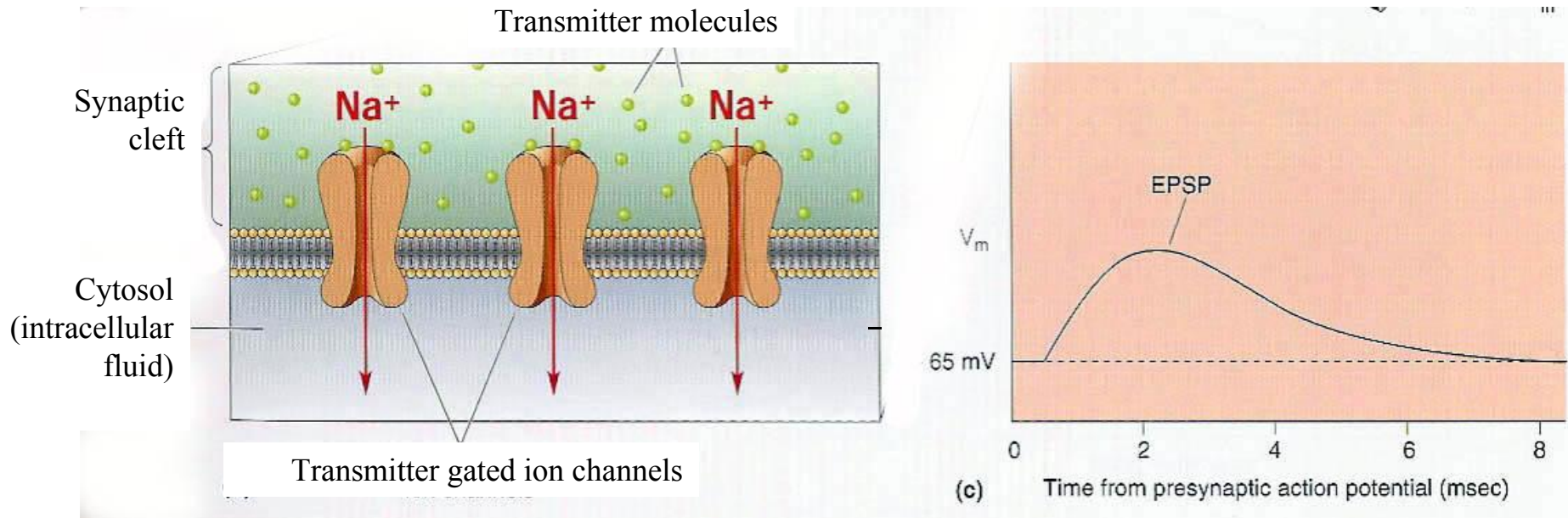
- **Amino acids.** Some amino acids found in foods, like ***glutamate*** or ***glycine***, can directly act as neurotransmitters.
- **Other amines.** These are synthesized by special enzymes from amino acid precursors. Examples: catecholamines (***noradrenaline***, ***dopamine***, ...) are synthesized from tyrosine. ***5-HT***, also known as ***serotonin***, is synthesized from tryptophan. To test whether a neuron uses one of these transmitters, scientists may look for the presence of the enzymes required for their synthesis.
- **Peptide neurotransmitters.** Like short protein-chains, require gene transcription for their synthesis. Examples: ***enkephaline***, ***substance P***.

This list is not exhaustive!

Neurotransmitter action

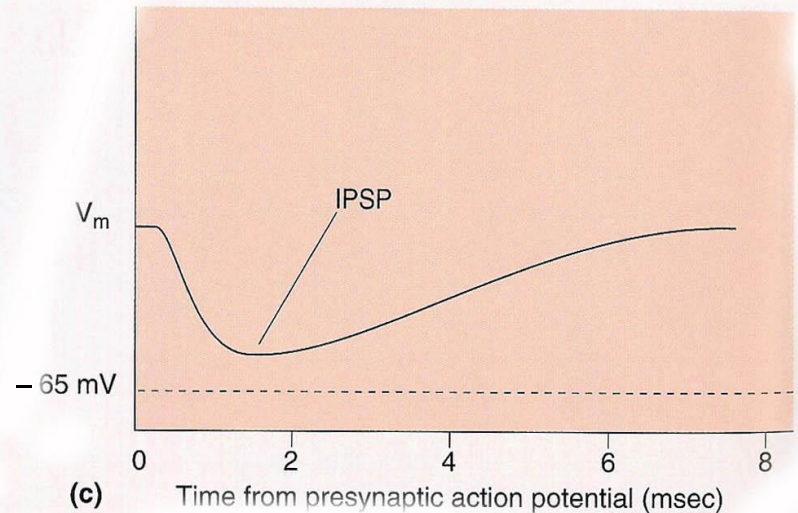
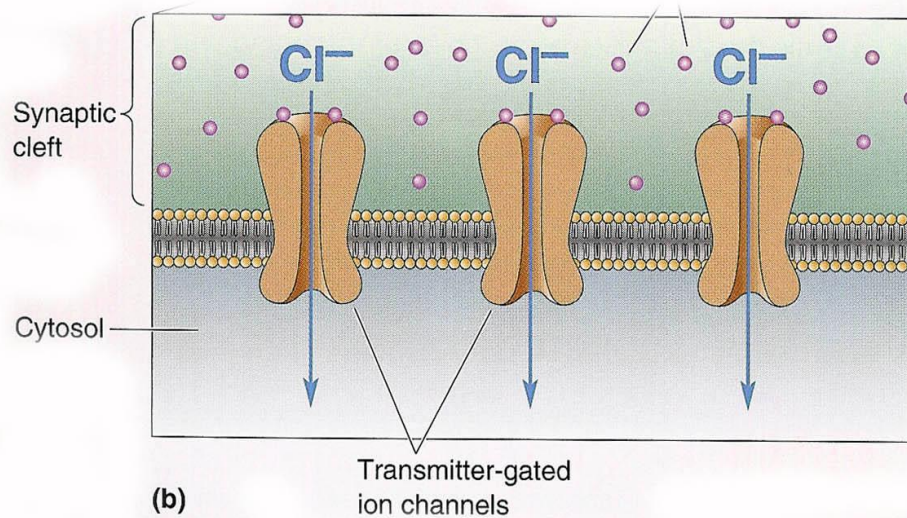
- The effect that a neurotransmitter has depends not so much on the chemistry of the transmitter, than on the properties of the receptors it binds to.
- *It's not the key that matters, but the door that is being unlocked.*

Excitation



- Excitation is achieved when neurotransmitter opens channels permeable to Na^+ or Ca^{++} , leading to a current *influx* and a depolarising *excitatory post synaptic potential* (EPSP).
- Typical examples: AMPA or NMDA receptors at a glutamatergic synapse.

Inhibition

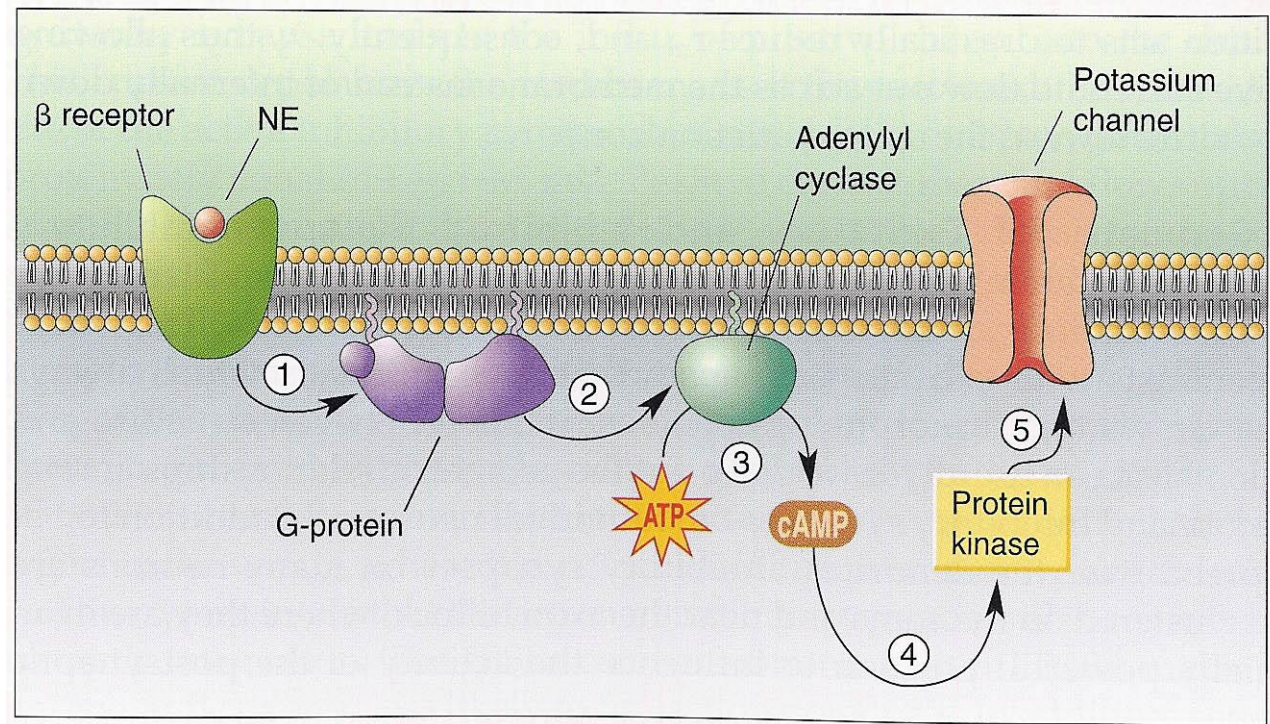


- One way to achieve inhibition is to open channels which are selectively permeable to Cl^- . This allows an influx of negative charge into the cell, making it harder for the neuron to become depolarized.
- Typical example: GABAergic synapse.

Diversity of Neurotransmitter Receptors

- There are many different neurotransmitters, and to add to the complexity, most of these transmitters can act on several different types of receptors.
- Many of these receptors are themselves ion channels (***ionotropic*** receptors), but some act indirectly via *second messengers* (“***metabotropic***” receptors).
- A single synapse can contain both ionotropic and metabotropic receptors “side by side”.

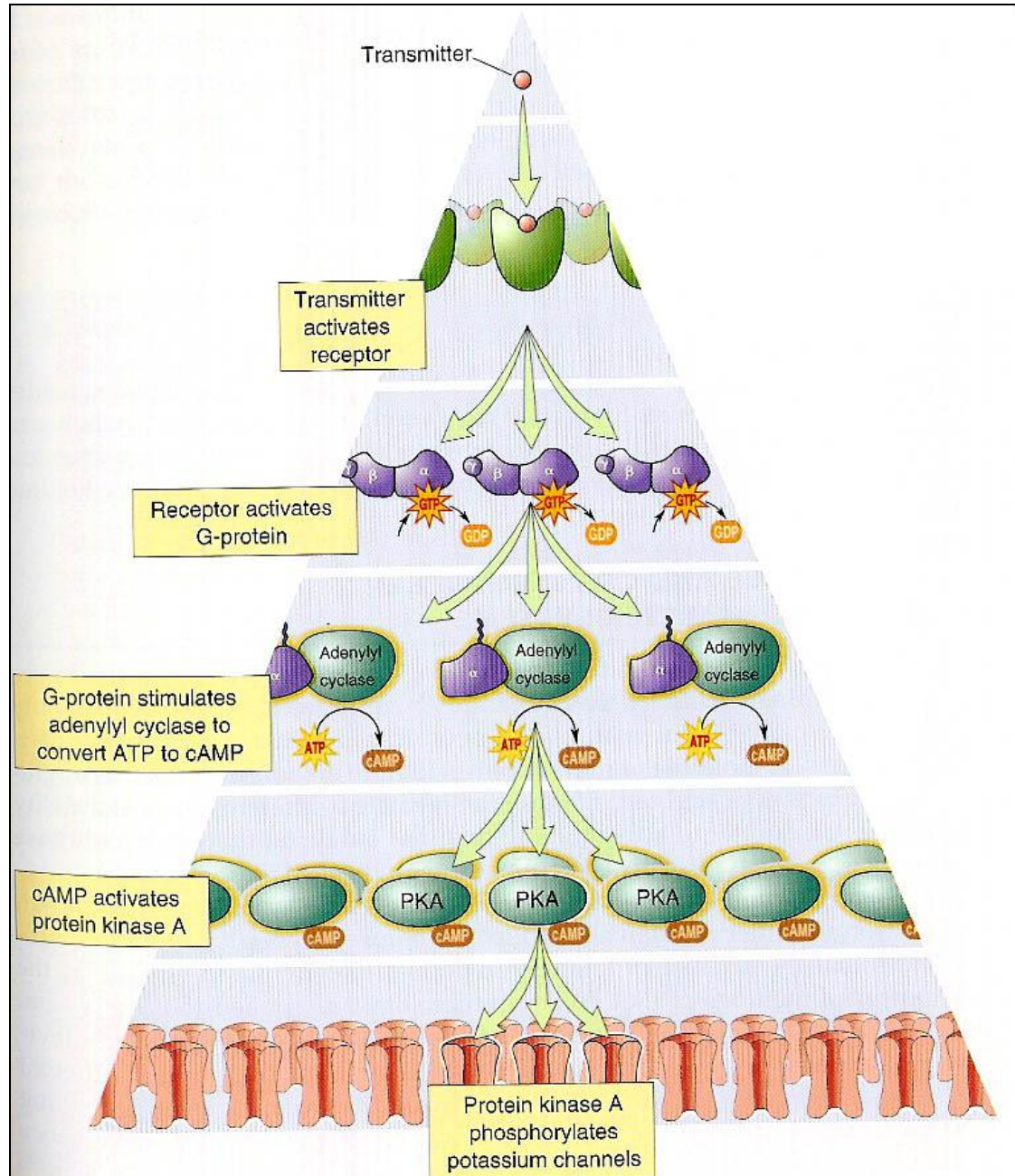
Metabotropic Receptors



- While metabotropic receptors are not ion channels themselves, they can, and often do, open or close ion channels indirectly via a *second messenger cascade*.
- The first step in the cascade is invariably the activation of a **G-protein**.
- There are different types of G-proteins, and they can trigger different things. In this example the G-protein activates *Adenylyl cyclase*, which in turn activates *protein kinase A*, which finally closes K^+ channels by *phosphorylating* them.

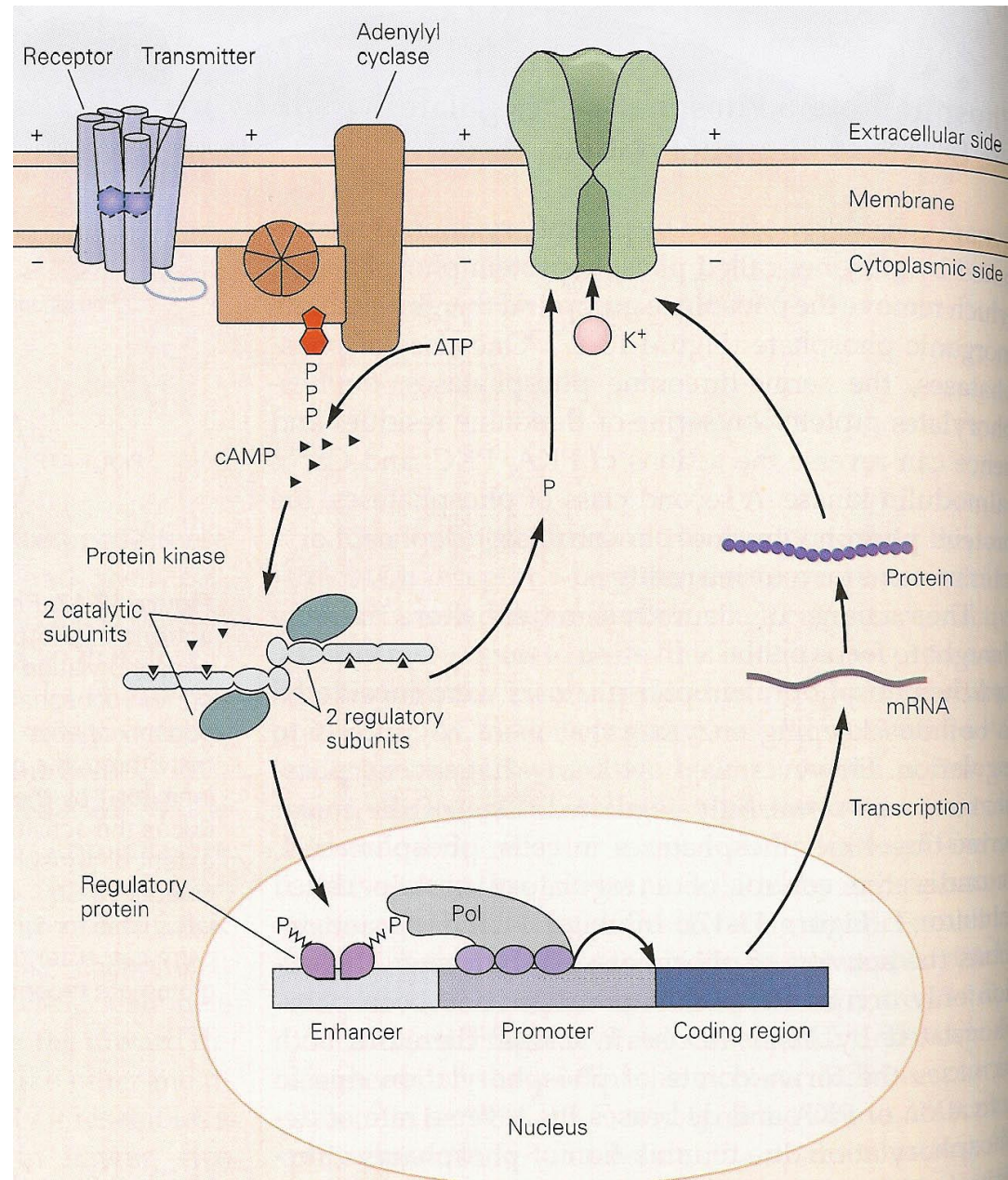
Second Messenger Cascades

Second messenger systems are costly and relatively slow, taking at least a few tens of ms. However, they can produce a considerable “amplification” of the signal, as in this example, where activation of only a few NE-beta receptors can eventually lead to the closure of a large number of K⁺ leakage channels.



Second Messenger Cascades - 2

Another advantage of 2nd messenger cascades is that they can achieve several things at once. For example, protein kinases may activate ***transcription factors*** in addition to any effect they have on ion channels. Consequently a neuron may react to stimulation of metabotropic receptors with a change in gene expression and the synthesis of new proteins.

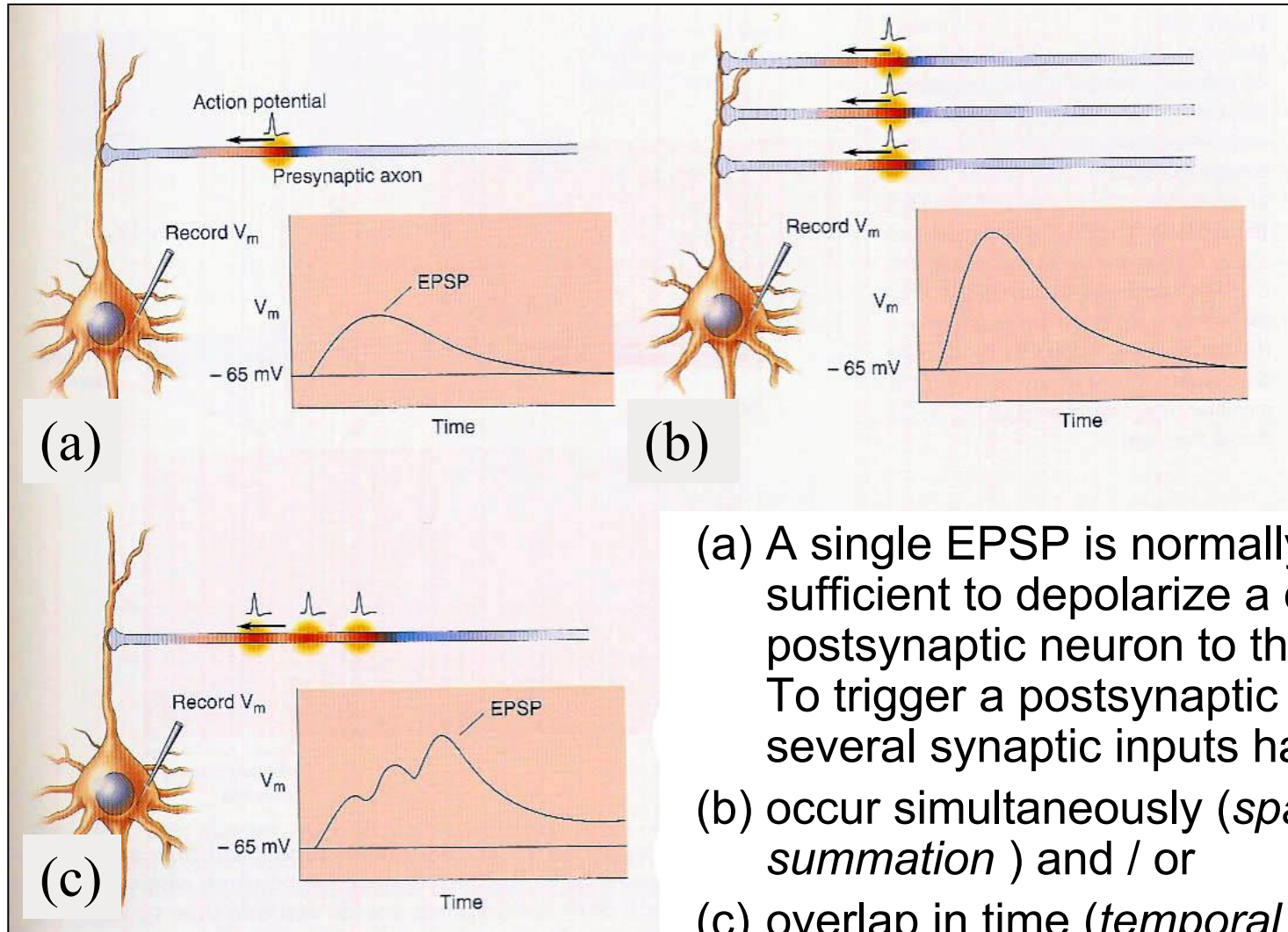


A Far From Exhaustive List of Neurotransmitter Receptors

Transmitter	Receptor	Action
Acetylcholine	nicotinic	ionotropic: K ⁺ Na ⁺
Acetylcholine	muscarinic	metabotropic
Glutamate	AMPA, Kainate	ionotropic: K ⁺ Na ⁺
Glutamate	NMDA	ionotropic: K ⁺ Na ⁺ Ca ⁺⁺
Glutamate	mGluR	metabotropic
GABA	A	ionotropic: Cl ⁻
GABA	B	metabotropic
Glycine		ionotropic: Cl ⁻
Dopamine	D1,..., D5	metabotropic
Serotonin (5HT)	5HT-3	ionotropic: K ⁺ Na ⁺
Serotonin (5HT)	5HT S	metabotropic
Norepinephrin	beta	metabotropic

Break

Synaptic Integration



- (a) A single EPSP is normally not sufficient to depolarize a central postsynaptic neuron to threshold. To trigger a postsynaptic AP, several synaptic inputs have to:
- (b) occur simultaneously (*spatial summation*) and / or
- (c) overlap in time (*temporal summation*).

Inhibition and Synaptic Arithmetic

- Post-synaptic neurons can carry out a sort of synaptic “arithmetic”, subtracting inhibitory currents from excitatory ones to achieve a net depolarization which may or may not be strong enough to make the post-synaptic neuron itself fire an action potential.
- Neurons as “decision makers” constantly ask themselves: does total excitation minus total inhibition (minus resting leakage) depolarize the axon hillock sufficiently to start an action potential? (“Leaky integrate and fire model”)

Excitatory / Inhibitory Balance

- In the brain, excitatory synapses outnumber inhibitory ones about 5 to 1. But:
- Inhibitory synapses can create larger hyperpolarizing currents, and are often found on the soma, near the axon hillock, where they can be most effective.
- Since one glutamatergic neuron in cortex delivers excitatory inputs to many thousand other neurons, and given that neural networks often form feedback loops (A excites B but B excites A), fast and effective inhibition is required to stop the brain becoming “overexcited” (epileptic).
- Some tranquilizers and anti-convulsant drugs work by potentiating inhibitory neurotransmission (e.g. benzodiazepines and barbiturates).

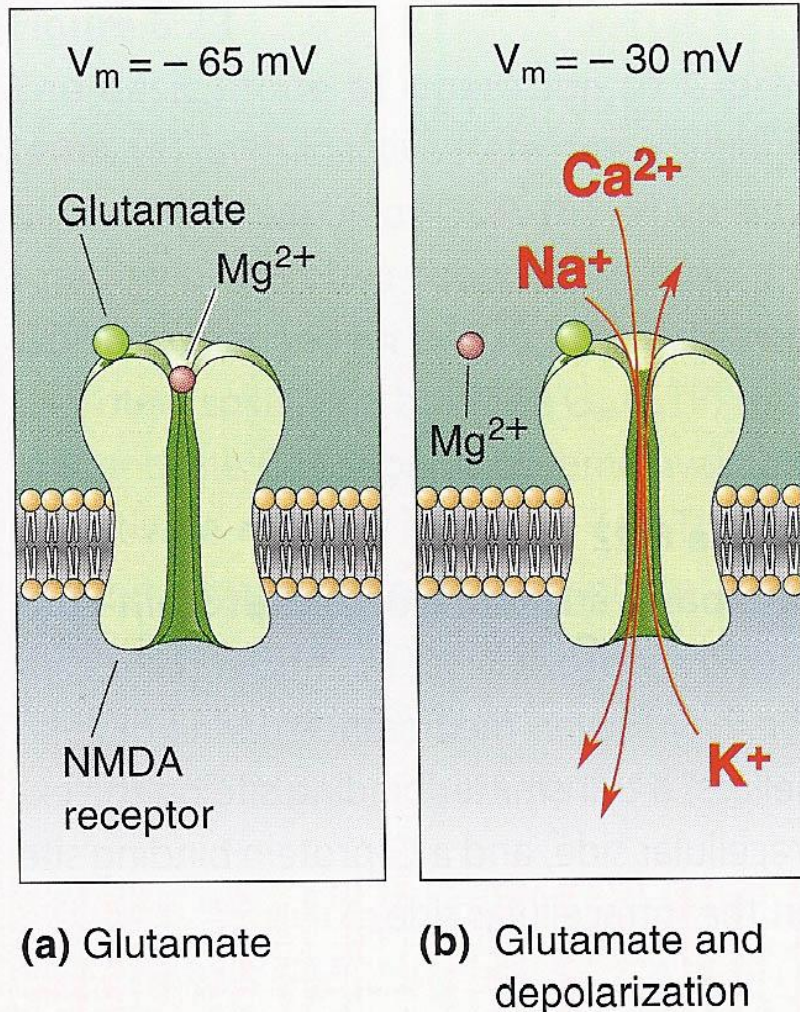
Synaptic Plasticity

- Central synapses can be “plastic”: they may change their *synaptic strength* (i.e. the size of the EPSC or IPSC) as a function of the recent, or not so recent, history of activity at that synapse.
- Neurophysiologists distinguish:
 - ***short term plasticity*** , phenomena like “paired-pulse depression” and “paired-pulse facilitation” which may last a few seconds to minutes,
 - and ***long term plasticity*** which lasts for at least several hours, but perhaps as long as many years.
- **Long-term potentiation (LTP)** and **long term depression (LTD)** are likely to form the basis of learning, memory and adaptive changes in the brain.
- LTP may also play a role in certain pathologies, like epilepsy (“kindling”)!

Long-Term Potentiation and Associative Learning

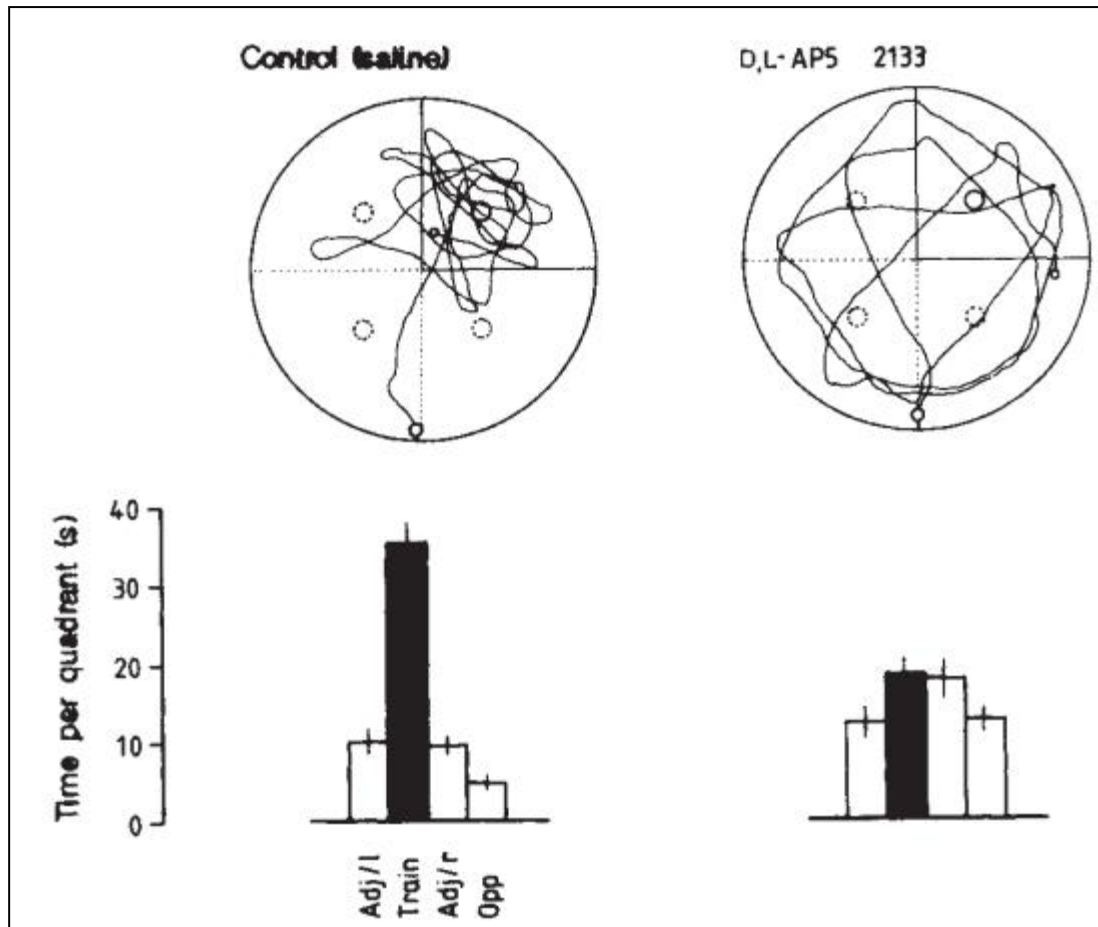
- The conditioned reflex, e.g. Pavlov's dog, is a simple example of associative learning.
- LTP was first demonstrated in a serotonergic synapse in the sea slug *aplysia*, where it mediates conditioned gill withdrawal. (Nobel prize to Eric Kandell)
- In vertebrates, LTP has been studied mostly in glutamatergic synapses, particularly in the hippocampus, but also neocortex and tectum (roof of the midbrain).
- LTP appears to obey the “**Hebb rule**”: synapses are strengthened only if their activation coincides with postsynaptic depolarisation from another source. It may form a “memory trace” of the coincident occurrence of conditioned and unconditioned stimuli.

The NMDA Receptor



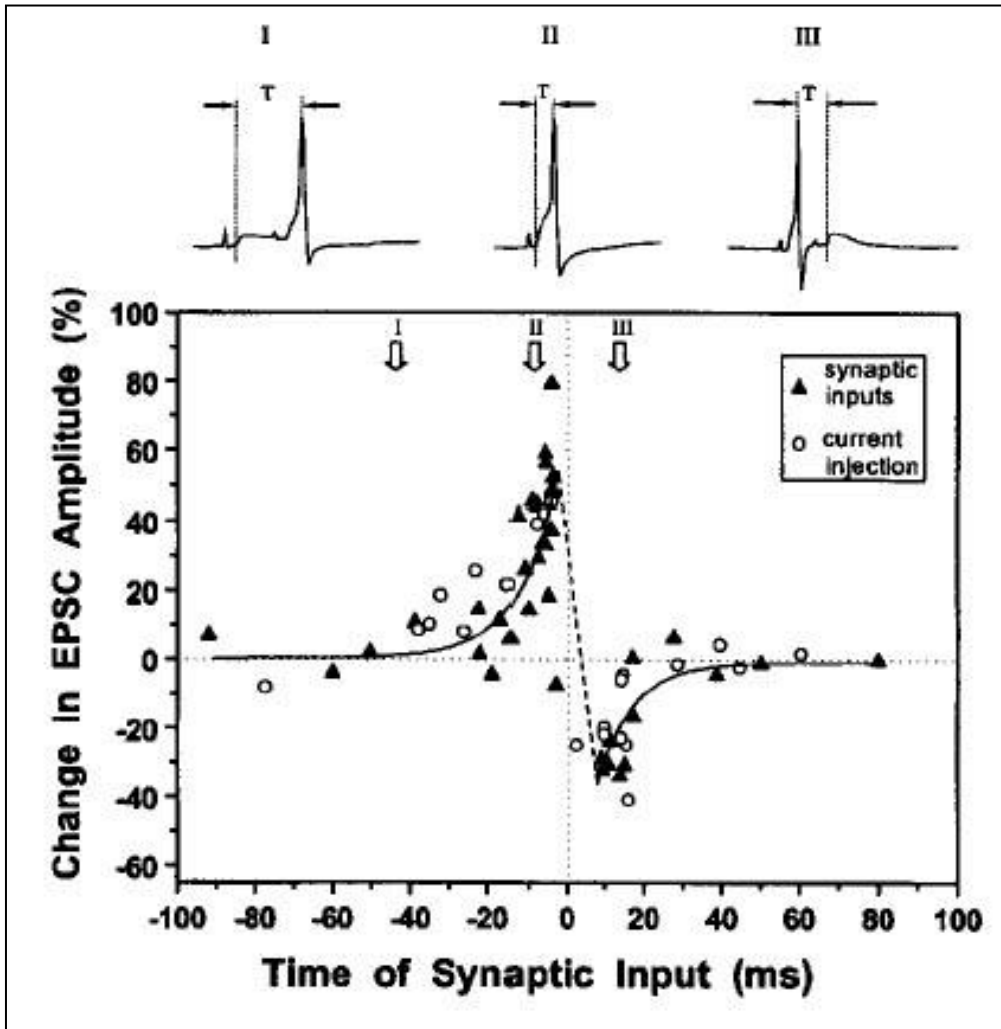
- NMDA receptors appear to be critically involved in LTP at the glutamatergic synapse.
- NMDA receptor channels open only if glutamate binds AND depolarisation removes a Mg^{++} from the channel's pore.
- Drugs that block the NMDA receptor (AP-5, MK-801, ketamine) prevent LTP.

NMDA receptor antagonists can impair the ability to learn



- Rat ventricles injected with either saline (control) or NMDA antagonist AP5.
- Rats trained in Morris water maze task.
- Control rats learn to remember where the submerged platform is, AP5 rats don't.

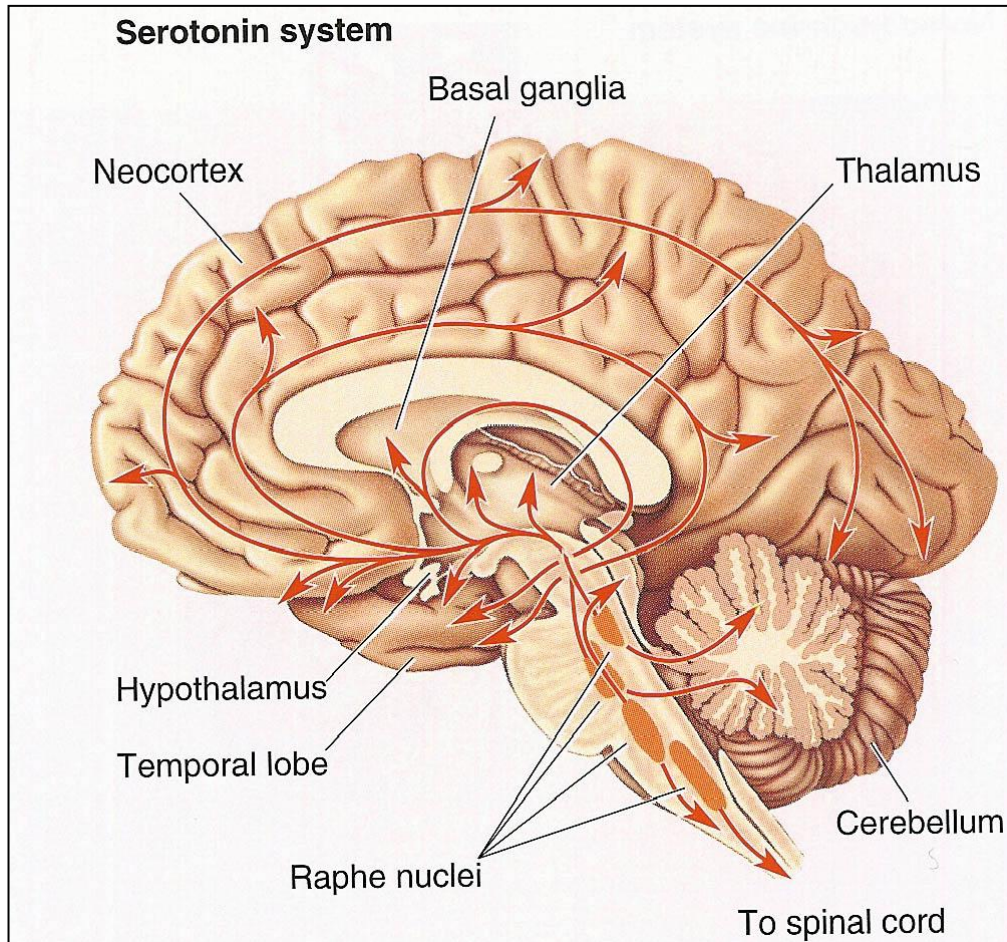
Time Dependence of LTP and LTD (Spike-timing dependent plasticity: STDP)



- EPSCs recorded from frog tectal cell in response to stimulation from two separate sites on the retina. One site stimulated supra-threshold, the other sub-threshold.
- If the sub-threshold stimulus follows the supra-threshold stimulus by a few ms, it is potentiated, otherwise it is depressed.

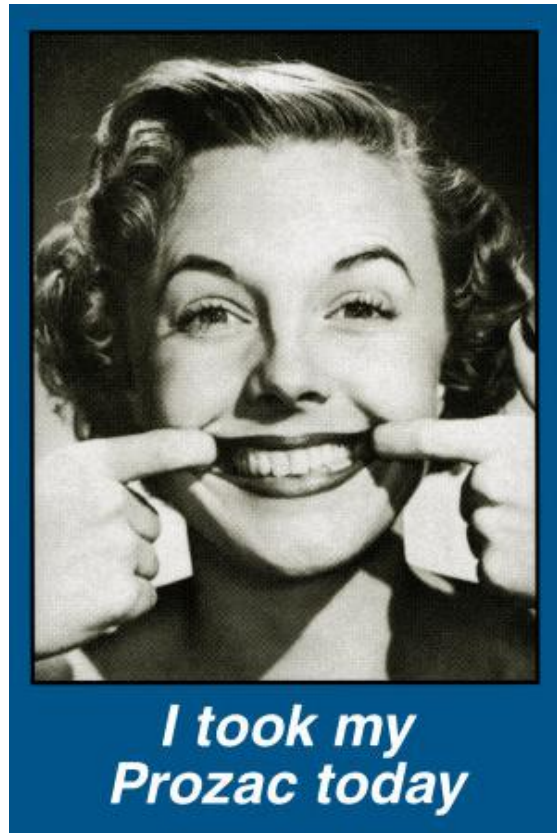
Zhang et al *Nature* **395**, 37-44 (1998)

“Diffuse” Transmitter Systems



- Most neurotransmitters most of the time are used to deliver “local” messages across the synaptic cleft.
- Some transmitters appear (also !) to be involved in widespread (“diffuse”) connections that regulate “global” states of the nervous system (mood, attention,...).
- For example, diffuse **serotonergic** projections from the **Raphe** nuclei (left) are thought to play a role in mood and mood disorders (e.g. clinical **depression**), as well as gating **pain** perception at the level of the spinal chord or above.

PROZAC - an international bestseller



- The antidepressant **Prozac** is a selective serotonin reuptake inhibitor (SSRI)
- It is thought to lift depression by causing serotonin to stay in the synapse for longer

Diffuse Transmitter Systems – 2

- Other diffuse transmitter systems include:
 - the ***norepinephrin*** (NE) system radiating out from the ***locus coeruleus*** (thought to modulate ***arousal*** and gates pain – “flight, fright, fight”)
 - the ***dopaminergic*** neurons of the ***ventral-tegmental area*** and the ***substantia nigra*** (“***reward*** centers” ?)
 - the ***cholinergic*** brainstem nuclei, like the ***nucleus basalis*** and the ***medial septal nuclei***, which may play a role in gating ***attention*** and facilitating ***learning***.

Recreational Drugs and Drugs of Abuse

- Some recreational drugs and drugs of abuse are believed to work through the diffuse systems. E.g.:
 - **cocaine** prevents dopamine re-uptake, potentiating **dopaminergic** activation,
 - MDMA (3,4-Methylenedioxymethamphetamine, “**Ecstasy**”) not only inhibits **serotonin** re-uptake, but reverses it, causing a substantial increase of serotonin levels at the synapses, which is thought to cause the feelings of euphoria reported by users.
 - **nicotine** is a powerful **cholinergic** agonist.
 - **cannabis** contains a compound that activates **anandamine** receptors.

Poisons and the Neuro-Muscular Junction

- Unlike synapses in the CNS, the NMJ is not protected by the blood-brain barrier. This makes it an easy target for numerous poisons:
- Curare, α -bungarotoxin and *clostridium botulinum* toxin (“**botox**”) block the AChR, causing “flaccid” paralysis by preventing the initiation of muscle APs.
- **Nicotine** (an ACh “agonist”) stimulates AChR and can cause “rigid” paralysis, triggering muscle spasms by inducing many “unwanted” muscle APs.
- “**Nerve gas**” (e.g. sarin) blocks acetylcholinesterase. Consequently ACh remains active in synaptic cleft for far too long, leading to rigid paralysis. (**Atropine** another ACh “antagonist” may be used as antidote).
- Some other ‘neuromuscular blockers’ (e.g. **pancuronium bromide**) are used clinically to prevent muscles twitching during surgery.

No Silver Bullet

- Countless drugs and medicines work by interfering with neuro-transmitter systems, and can have very powerful, and sometimes beneficial effects.
- However, because the same neurotransmitter often have several different actions at different places in your brain or body, such drugs have numerous side effects:
- Nicotine may help concentration, but can also cause diarrhoea and insomnia.
- Halperidol can calm psychotic patients, but produces Parkinson's-like stiffness and apathy.
- Amphetamine can relieve fatigue and improve concentration, but can also trigger dangerously high blood pressure, anxiety and paranoia, and can cause addiction.