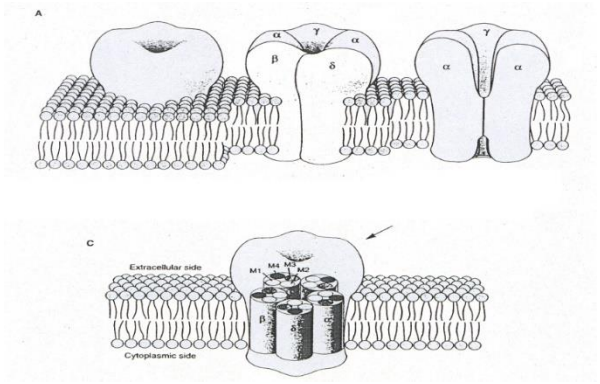
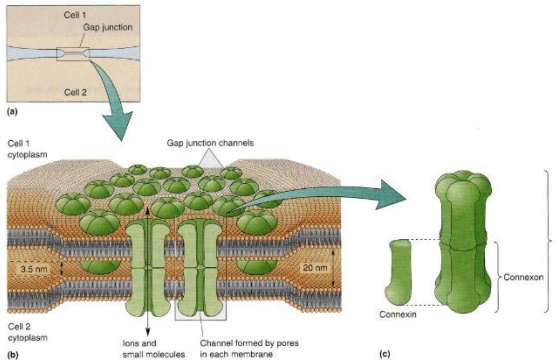
Chemical & Electrical synapses

Neural network organization is accomplished by synapses which allow communications between neurons

There are two strutturally and functionally different types of synapses:

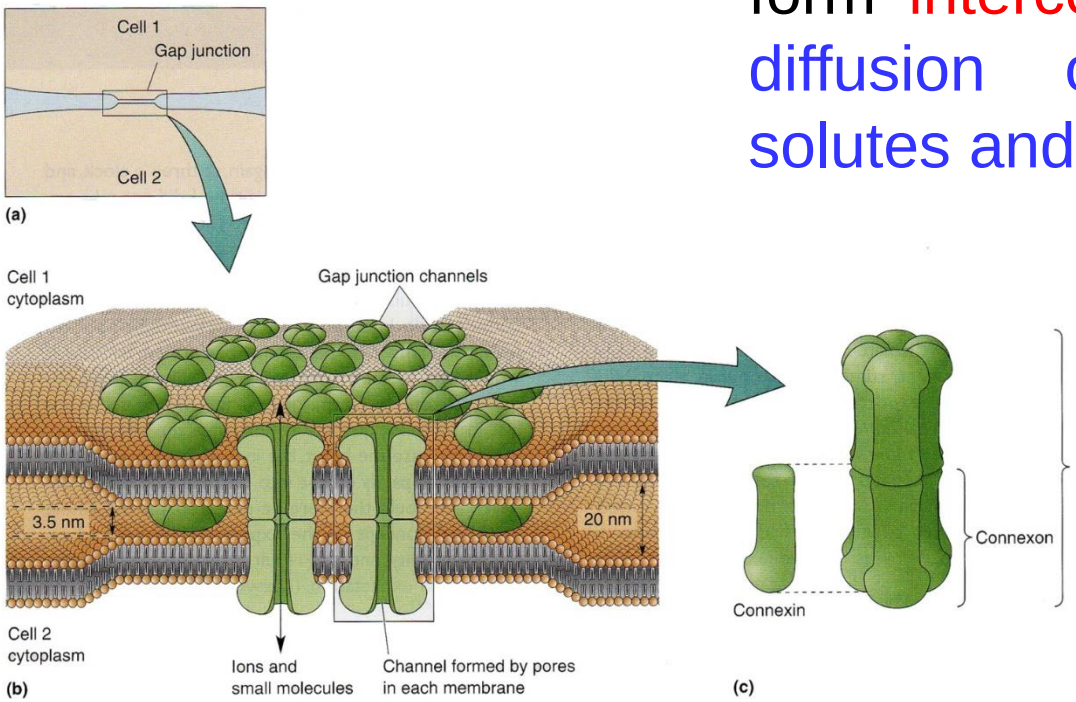


Chemical
(Ligand-gated channels)



Electrical
Gap junctions

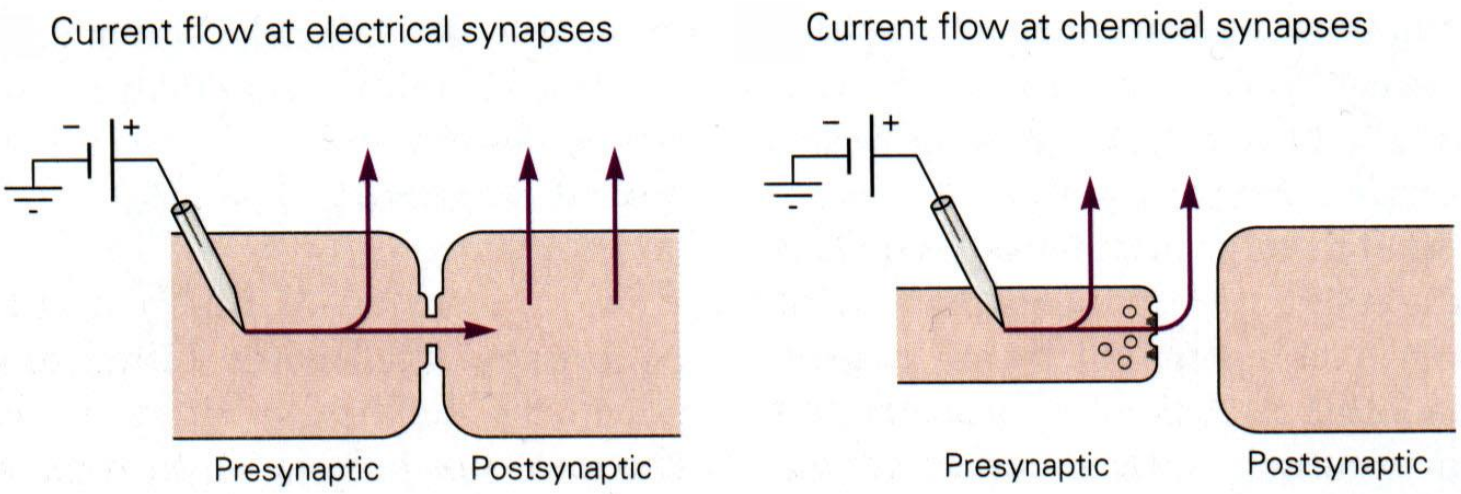
Six Connexins combine to form a hemichannel called connexon. Two connexons that span the opposing membrane of two cells align to form intercellular channels for the diffusion of small intracellular solutes and ions.



Gap junctions are integral membrane proteins that enable the direct cytoplasmic exchange of ions and low molecular weight metabolites between adjacent cells

The electrical coupling: a low-resistance pathway supporting bi-directional communication.

Electrical synapses: high transmission velocity, stereotyped activity
Chemical synapses: excitatory and inhibitory action, more flexible

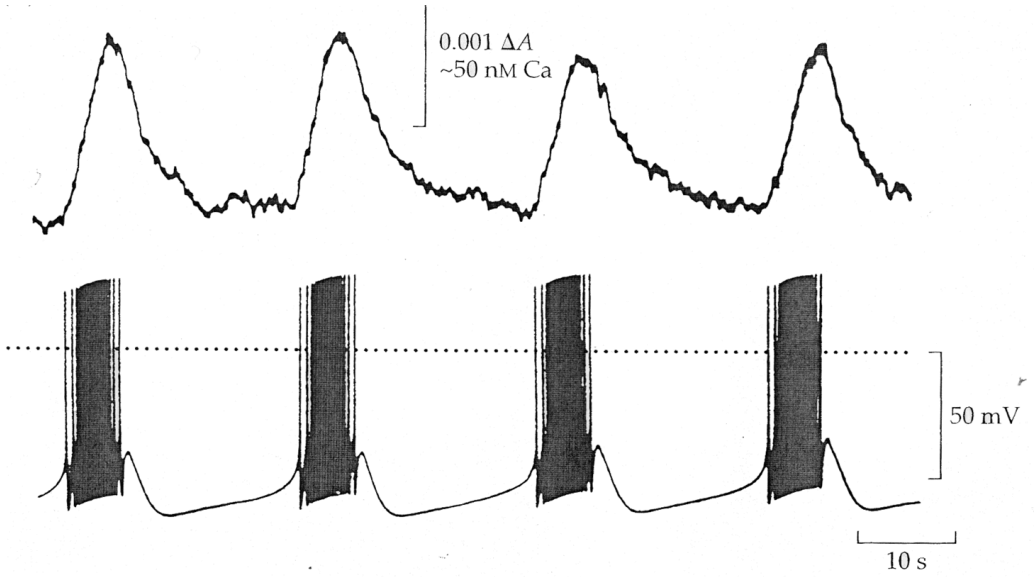


The exchange by gap junction is not specific, it involves ions, small metabolites with a MW up to 1 kDa (second messengers, aminoacids, nucleotides: ATP or ADP, Ca^{2+}, cAMP, IP_3).

Gap junction between neurons are particularly common during early embryonic stages.
During brain development, gap junctions allow neighboring cells to share both electrical and chemical signals that may help to coordinate their growth and maturation.

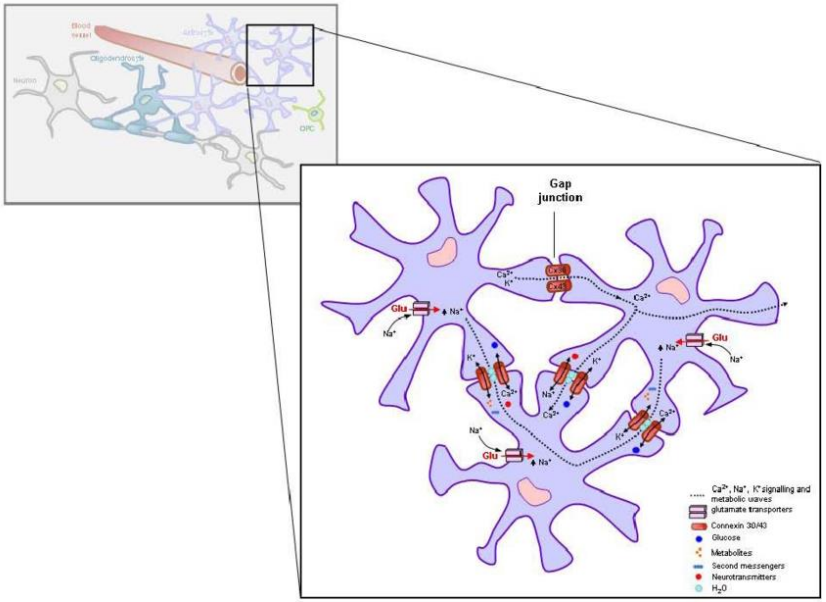
The number of connexins in cell-cell channels is regulated by controlling transcription, translation, trafficking, and degradation; and all of these processes are under strict control.

Gap junctions mediate sychronous activity



Synchronous activity of different neurons may give higher functional information than those given by trains of action potentials in single neurons.

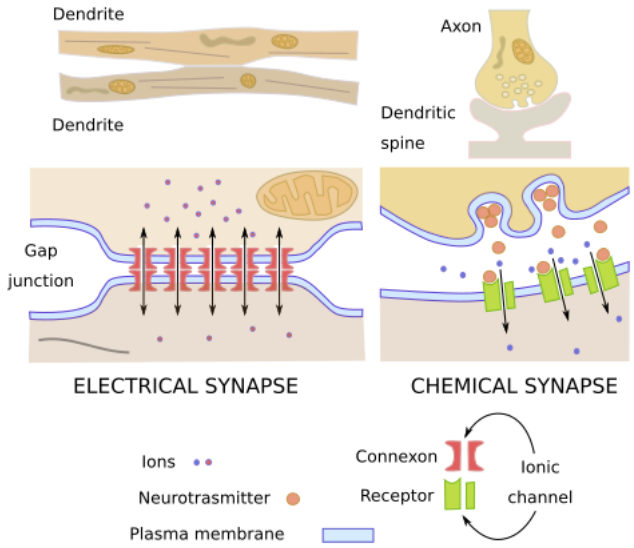
Gap junctions play a particular role in astrocytes, where they allow the coupling of astrocytes to each other, to form networks in which cells can exchange signals mediated by calcium waves



In contrast to chemical synapses, located at axonal boutons, electrical synapses can be found to couple various neuronal compartments and processes.

Most neuronal gap junctions in the mammalian CNS appear to be located between distal dendritic processes.

Gap junctions between axons have a stronger influence on neuronal synchronization.



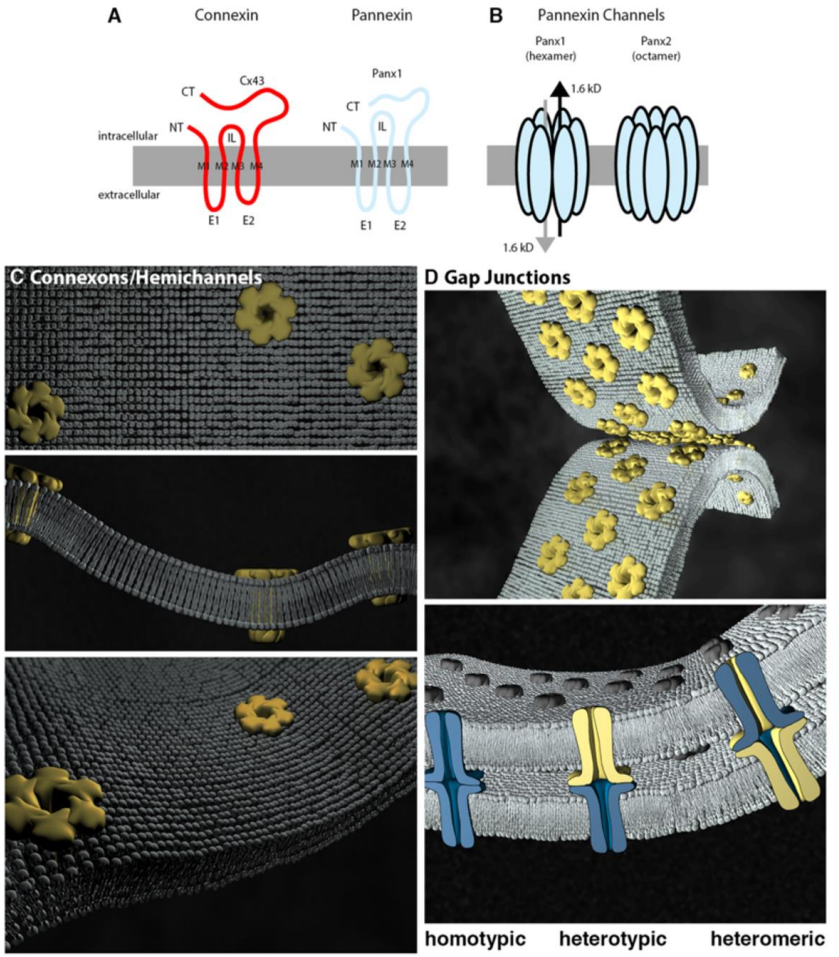
Pannexins

Connexins (Cx) and pannexins (Panxs) share some structural similarities but no sequence homology.

Panx forms channels in non-junctional membranes and are not intercellular channels.

They release ATP, IP_3, ions, AA. Often they are identified pharmacologically (carbenoxolone).

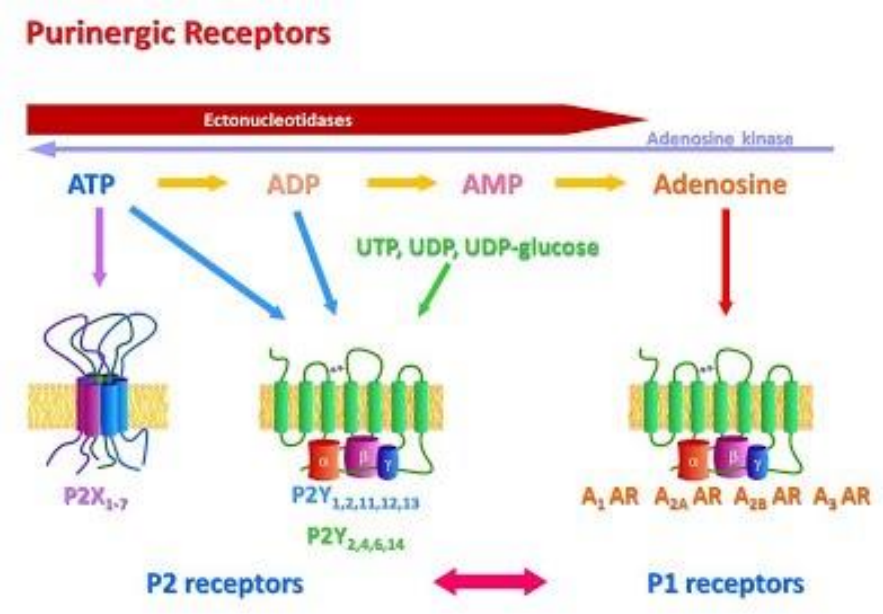
They can be activated by membrane depolarization, extracellular potassium, intracellular calcium, tyrosine phosphorylation or mechanical stretching via unknown mechanisms.



Swayne & Bennett, 2016

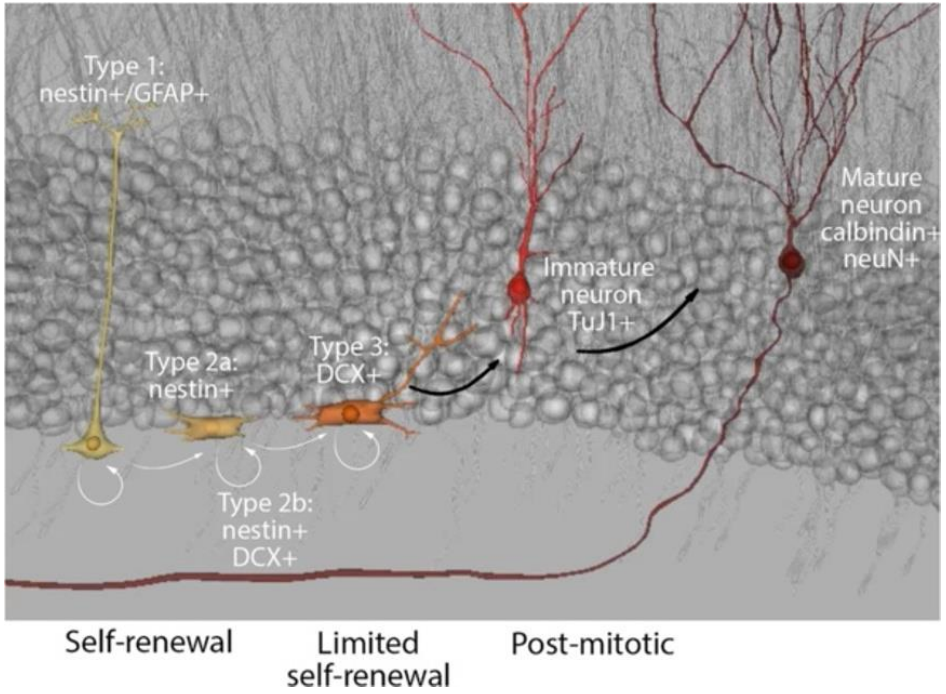
ATP is not only an intracellular energy source it acts also as an extracellular signalling molecule

Critical autocrine and paracrine signalling pathways are triggered by the action of the released ATP on various ATP-sensitive purinergic receptors involved in a great variety of either physiological or pathological processes such as mechanosensory transduction, central control of autonomic functions, glia-glia and neuronal-glial interaction, pain, trauma, ischemia or inflammation, epilepsy, AD



Adenosine: P1 R / A1, A2A, A2B, A3
A1 and A3 negatively coupled to AC
A2A and A2B positively coupled to AC

Pannexins have been implicated in mediating ATP release from neuronal progenitor cells, neurons and glial cells.



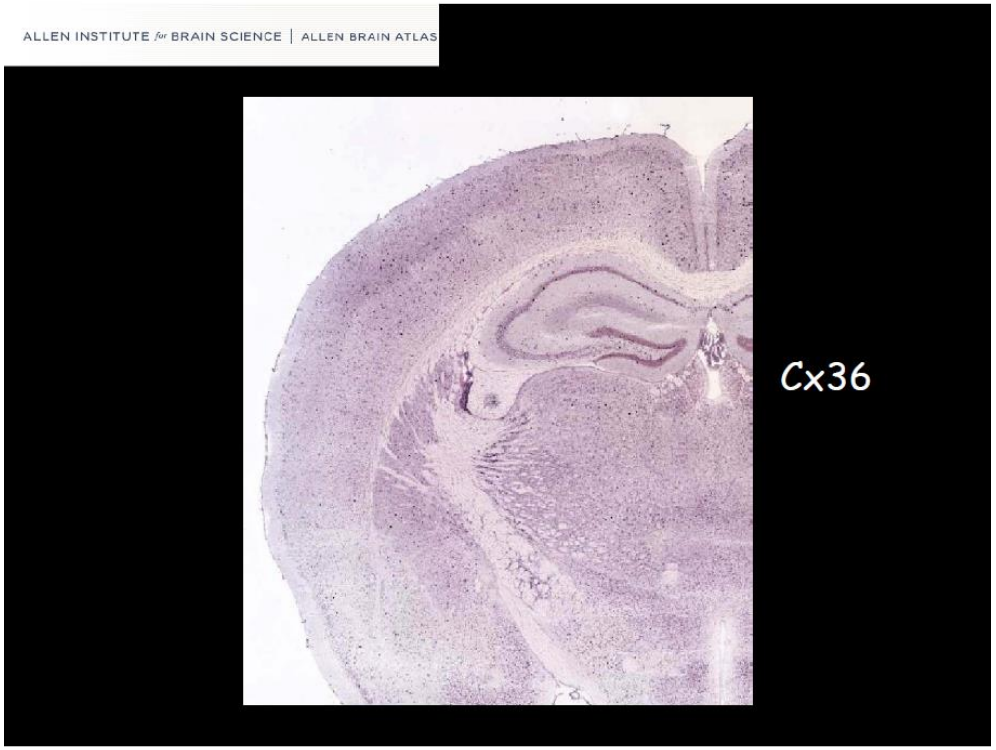
Gap junction detection

Immunofluorescence detection: Dye coupling

Electron microscopy: dendro-dendritic and dendro-somatic "close appositions"

Paired recording reveals directly the presence of electrical synapses among identified cell types.

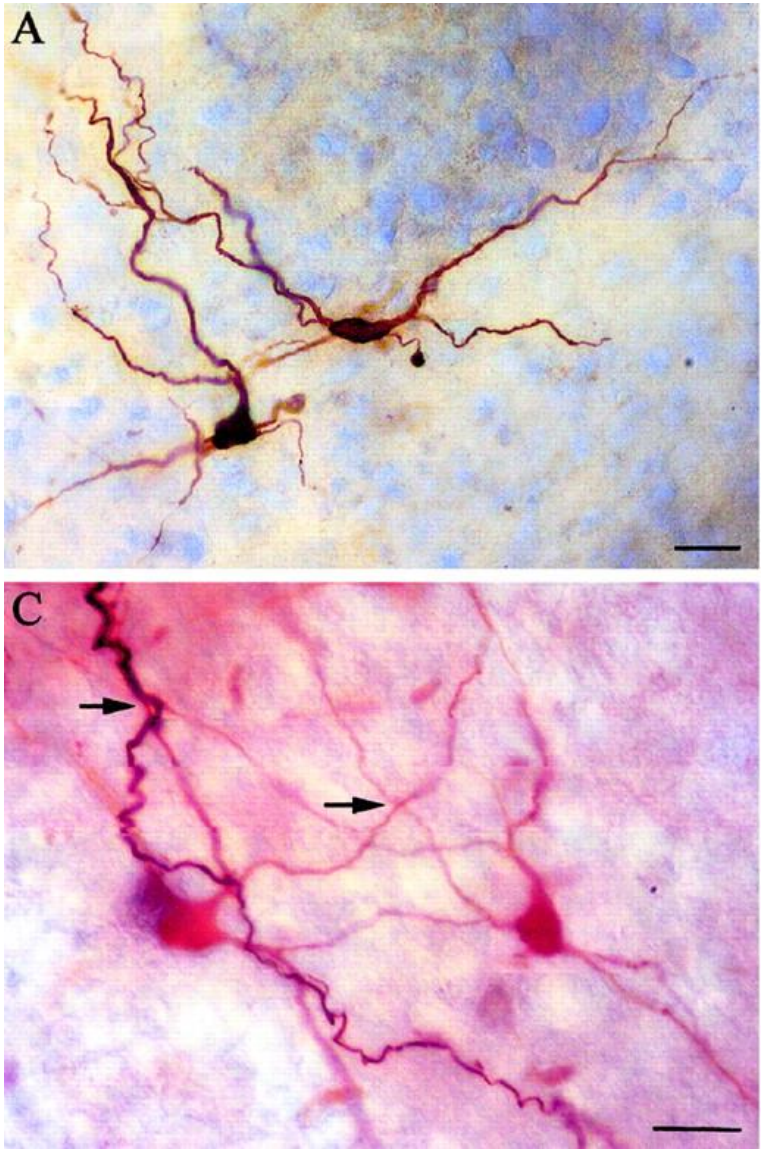
Immunofluorescence detection



20 different connexins have been identified in mice:
Cx26, Cx32, Cx36, Cx43, Cx47; 14 expressed in CNS.
In the neocortex, gap junctions are expressed at very early developmental stages, and they are involved in many processes such as neurogenesis, neuronal migration and synapse formation.

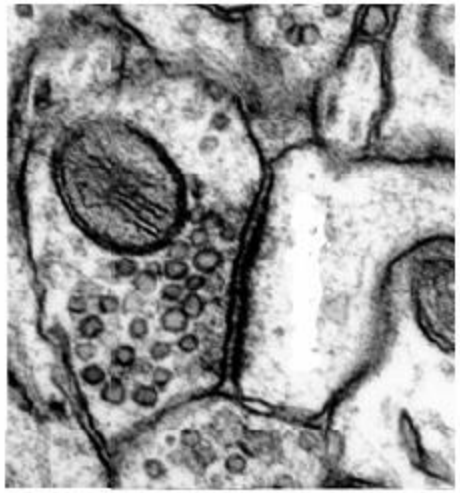
Dye coupling suggests the presence of gap junctions

Neurobiotin
Lucifer yellow

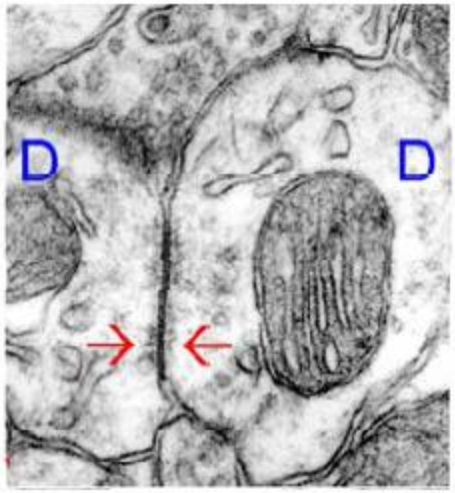


Electron microscopy

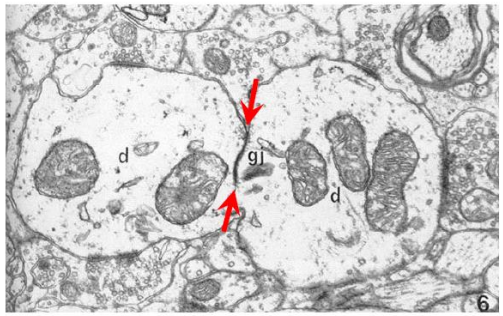
Chemical synapse



Electrical synapse

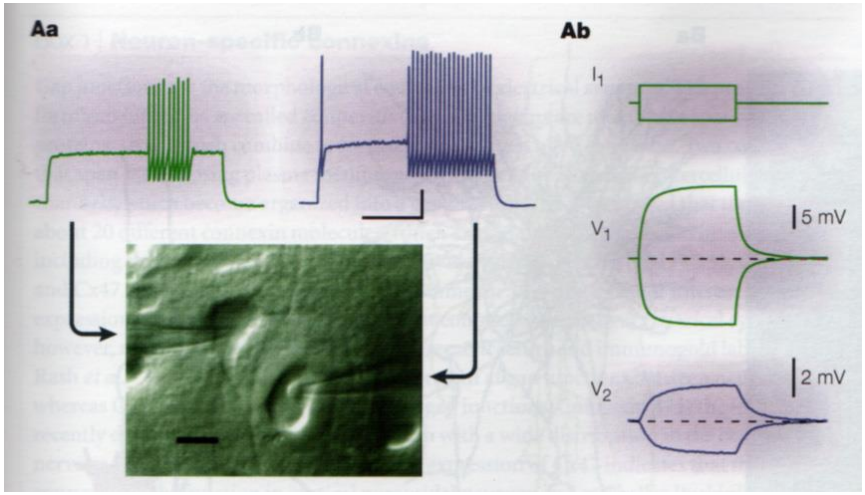


Gap junctions interconnect dendrites
in primate cerebral cortex



Sloper and Powell, *Proc Roy Soc Lond*, 1978

Pairs of electrically coupled neurons



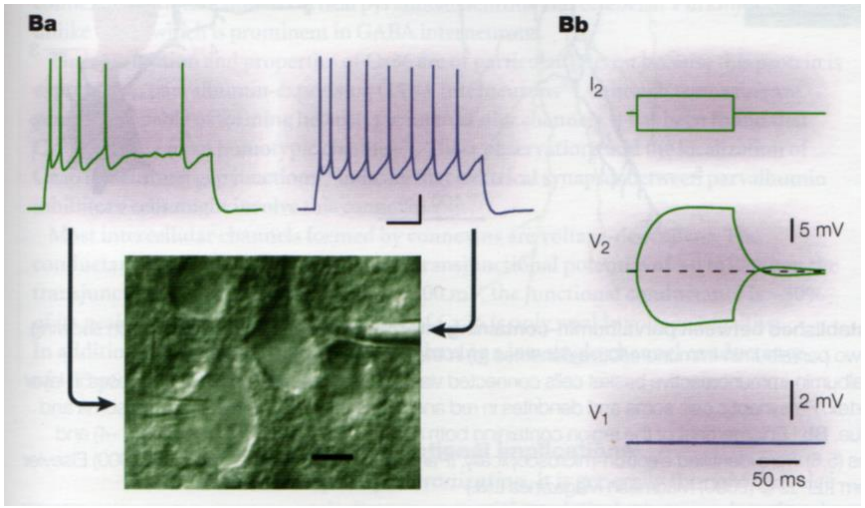
Galarreta & Hestrin, Nature Neurosci 2001

Fast spiking INT, PARV $^{+}$
are highly interconnected in the neonatal and adult cerebral cortex.

Coupling potentials present the same sign as presynaptic signals but are smaller in amplitude.

Due to the presence of chemical and electrical synapses neural networks are established that can have important implications for coordinating activity in cortical circuits.

PYR cells & Regular spiking:
no functional gap junctions



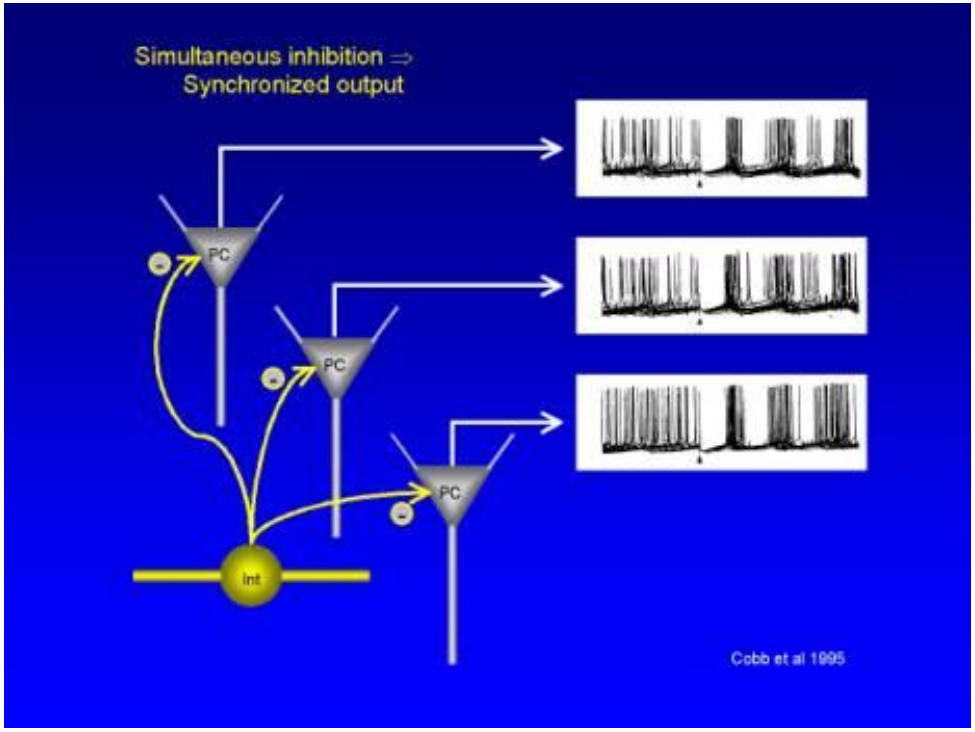
Galarreta & Hestrin, Nature Neurosci 2001

Gap junction regulation

Gap junctions can be modulated by phosphorylation, that can change their unitary conductance, the open probability or their internalization.

Intracellular pH and $[Ca^{2+}]_i$ might regulate the gap junction activity. Generally intracellular acidification and increase in $[Ca^{2+}]_i$ uncouple gap junctions

Networks of hippocampal GABAergic interneurons synchronize neuronal activity, driving a rhythmic inhibition and giving the *output of pyramidal cells*.



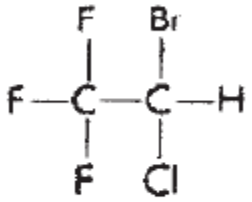
Extensive electrical coupling plays a role in detecting and controlling spike timing in the neywork.

Various types of injury induce an increase in neuronal electrical coupling

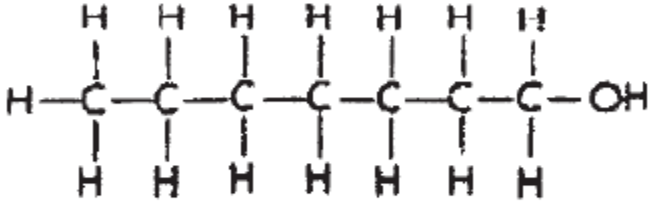
Ischemic, traumatic injuries
have been associated to a modulation of gap junctions by mGluR II (cAMP/PKA) activation or an increase in transcription level, respectively.

The knowledge of such complex system has important implications for developing treatments for deseases of neurodevelopment and brain injury.

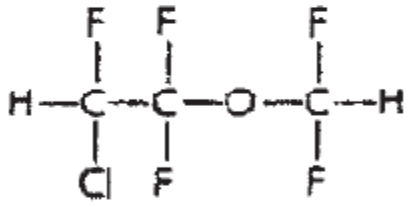
Many types of drugs block gap junction channels; nearly all of them lack specificity and potency



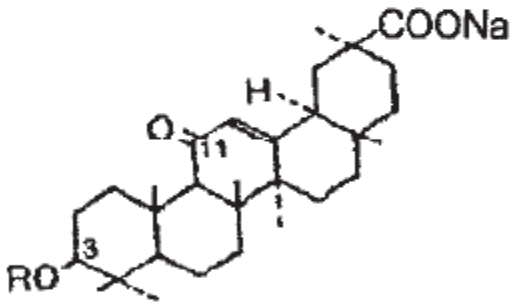
halothane



heptanol



enflurane

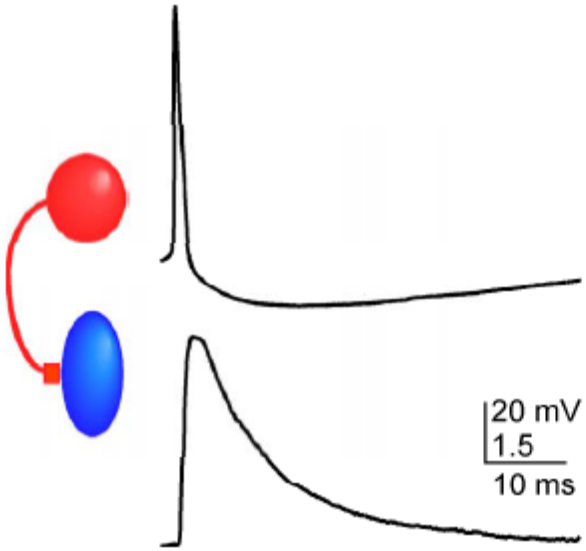


18-glycyrrhetinic acid (R=H)
carbenoxolone (R=$NaOOC(CH_2)_2CO$-)

Rozental, Srinivas, Spray, *Meth Molec Biol*, 2001

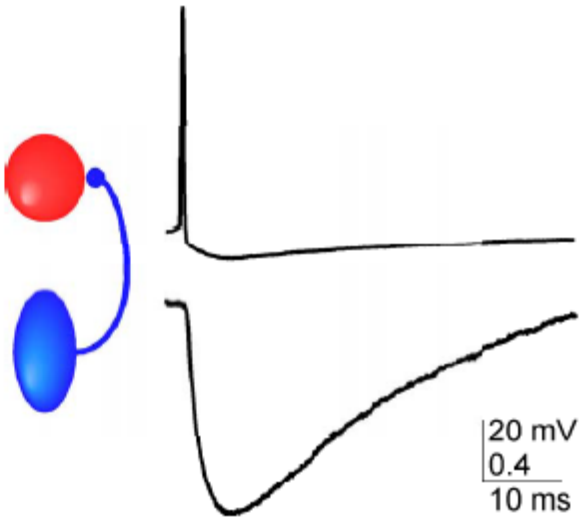
Chemical Synaptic Transmission

Excitatory



Excitatory postsynaptic potential (EPSP) is ***sign preserving*** (but only works in the depolarizing direction)

Inhibitory

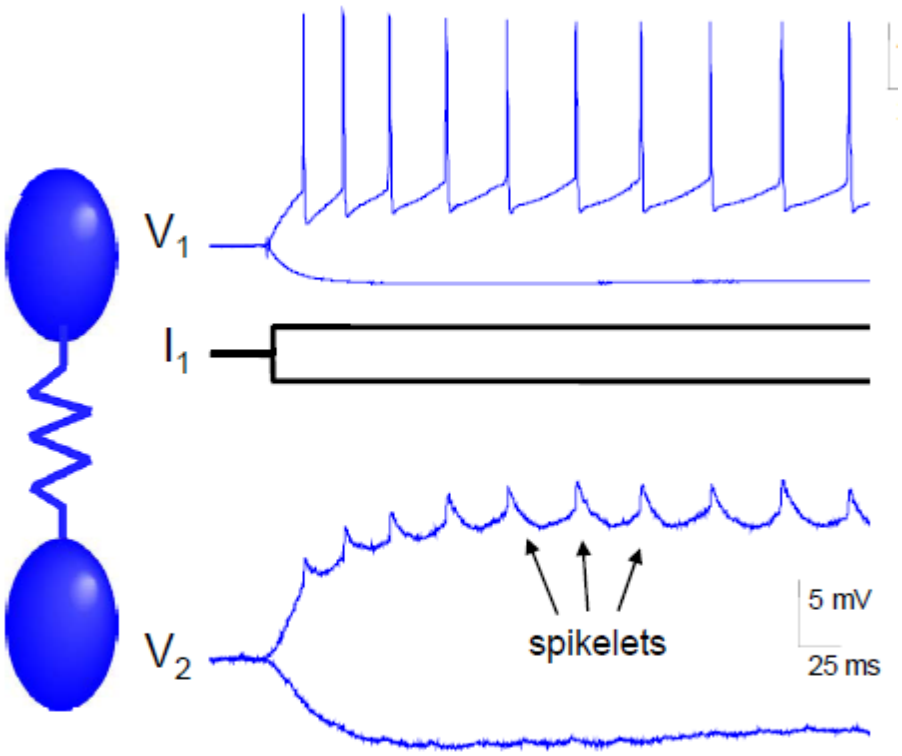


Inhibitory postsynaptic potential (IPSP) is ***sign reversing*** (and also works in only one direction)

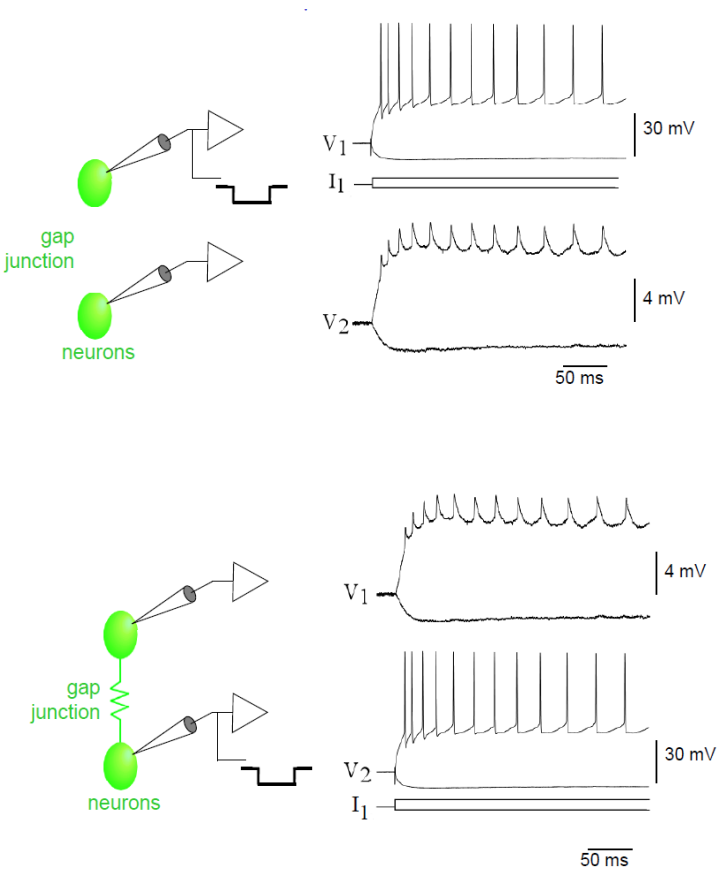
Why are most synapses chemical?

When pre- and post-synaptic elements are electrically coupled, a presynaptic spike of 100 mV would likely cause only 1-mV change in the postsynaptic cell because relatively little charge can flow through these junctions to change the large membrane capacitance of the postsynaptic cell.

Attenuated post-synaptic responses



Most electrical synapses are bidirectional and symmetrical



weak voltage-dependency in neuronal Cx

The strength of electrical coupling between neurons depends on:

1) the electrotonic distance

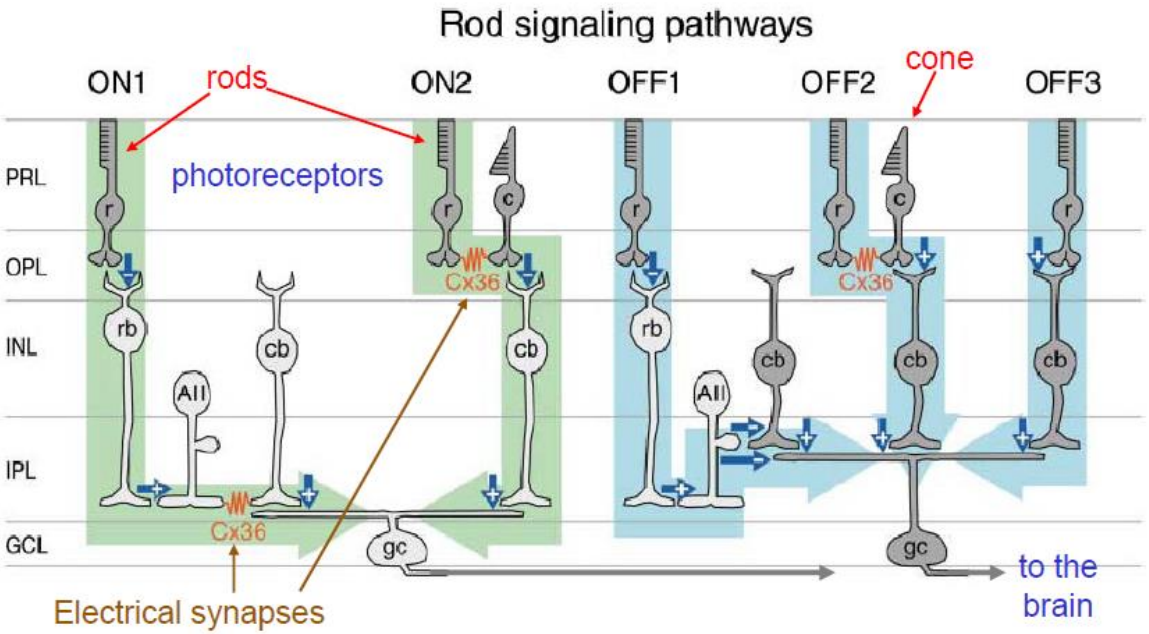
2) the R_m of the postsynaptic cell

3) The connexin density

What happens if you eliminate electrical synapses from the brain? (knock out the *Cx36* gene to find out)

- The mice are viable.
- Retinal deficits (total night blindness) (Deans et al., 2002)
- Impairment of fine motor control (Jutras, Burwell, Connors)
- EEG abnormalities (Buhl et al., 2003)
- Impairment in more “complex” motor learning tasks, object memory, and habituation (Frisch et al., 2005)
- Deficits of circadian behavior (Long et al., 2005)
- etc…

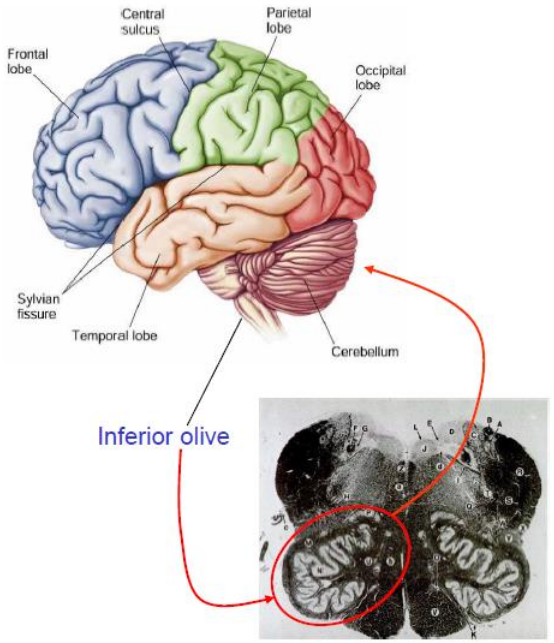
Visual inputs arrives with a wide range of light intensity. The retina's ability to respond flexibly is mediated in part by adjusting the conductance of gap junctions that interconnect all of the main types of retinal neurons

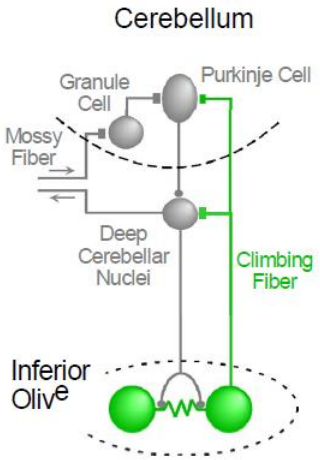


Demb & Pugh; after Deans et al., *Neuron*, 2002

Why do Cx36 knockout mice have problems with motor control?

Electrical synapses are important in neural circuits related to the cerebellum





Olivary neurons can no longer synchronize, coordination of muscle contraction is impaired («ataxia»).

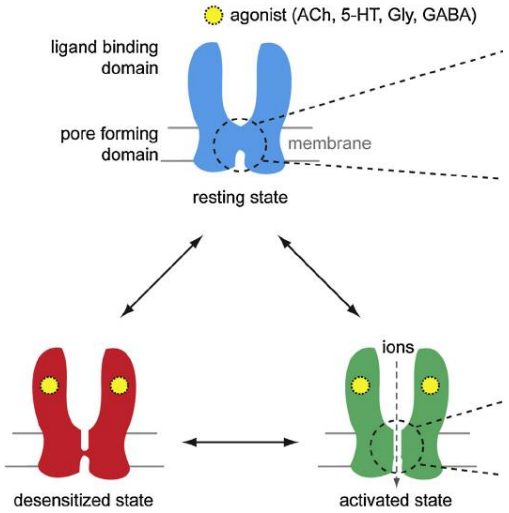
Benefits of chemical transmission

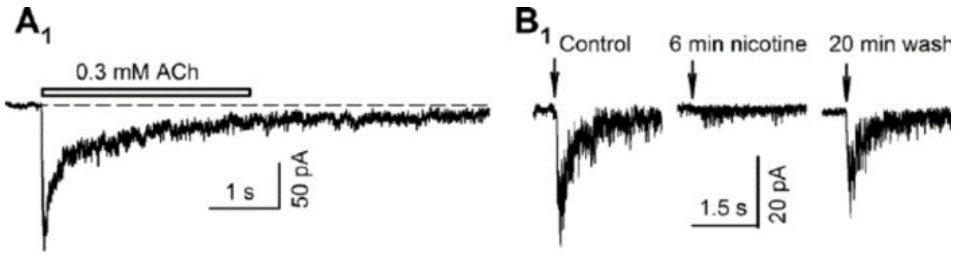
- Amplification
- Sign inversion
- Graded vs. all-or-none
- Varied temporal duration
- Multiple receptors with distinct properties
- Plasticity

Chemical synapses are characterized by high flexibility. Different afferents can have different effects with different strengths and time course on each other as well on postsynaptic cell.

The flexibility is essential for the complex processing of information that neural circuits must accomplish, and provides an important locus for modifying neural circuits in the adaptive processes as learning.

Most of ligand-gated channels have three main functional states in response to agonist: **closed**, **open**, **desensitized**





Brief exposure to high concentrations of neurotransmitter causes opening of the channel. After a couple of ms, the receptor closes to a non-conducting desensitized state. Phosphorylation,Ca^{2+}-dependent mechanisms?

For metabotropic receptors:
Phosphorylation can induce uncoupling (s, min)
Internalization (min)
Downregulation/degradation (hours, days)

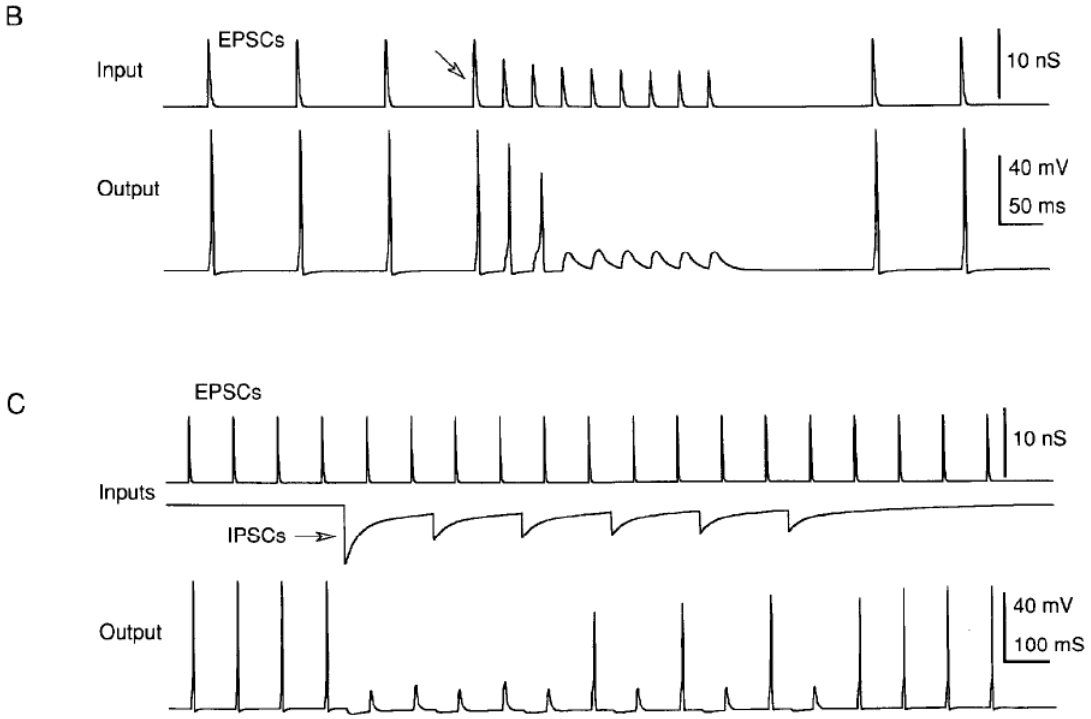


Fig. 5. ***Receptor-specific desensitization kinetics might have implications for neuronal-signal processing.*** **(A)** *A simple compartmental model illustrates the potential effects of synaptic desensitization on the input–output behavior of a neuron. Passive properties are assumed to be uniform throughout the cell, with specific membrane capacitance and resistivity of 1 $\mu F\,cm^{-2}$ and 100 $k\Omega\,cm^2$, cytoplasmic resistivity of 100 Ωcm, and a resting membrane potential of –65 mV. Hodgkin–Huxley-like Na^+ and K^+ currents and leakage currents are also present [E_{Na} = 50 mV, 50 $mS\,cm^{-2}$, soma only; E_K = –90 mV, 5 (dendrite) or 10 (soma) $mS\,cm^{-2}$; E_{leak} = –65 mV, 0–2 $mS\,cm^{-2}$, soma only]. Synaptic current kinetics and desensitization properties are from Refs 25 and 74. Simulations were run using Nodus 3.2 (Ref. 84).* **(B)** *Excitatory postsynaptic current (EPSC) desensitization. In the model neuron, each full-amplitude EPSC (expressed as conductance, upper trace) triggers an action potential (lower trace) when the frequency of release is 10 s^{-1}. However, when the frequency is increased to 30 s^{-1} (arrow), desensitization causes a progressive reduction in EPSC size until the resulting potential change no longer reaches the firing threshold. In the absence of desensitization, the following frequency approaches 100 Hz (not shown).* **(C)** *Inhibitory postsynaptic current (IPSC) desensitization. During continuous excitation (upper trace), a full amplitude IPSC (inverted in the middle trace, arrow) inhibits EPSC-driven spike firing (lower trace). Subsequent IPSCs (5 s^{-1}) are attenuated by desensitization, resulting in renewed spike firing despite the ongoing GABA release.*

Jones and Westbrook, 1996