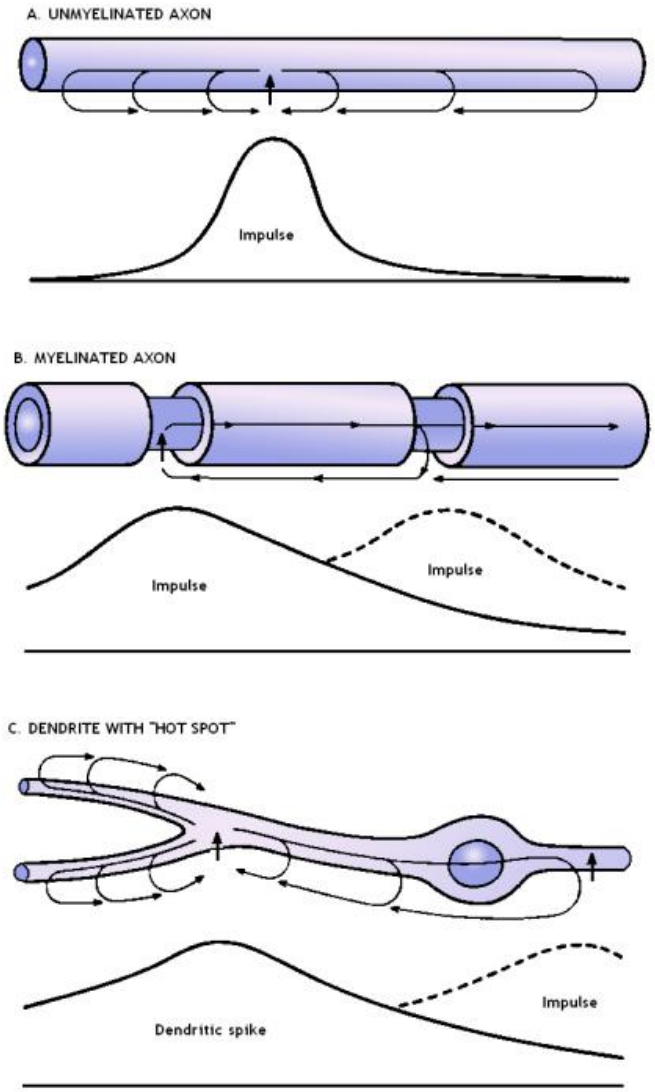
Conduction of the action potential



The current flowing into the cell has to flow back out to complete the circuit. It spreads along the fiber seeking pathways of least resistance. These currents spread the depolarization to neighboring membrane sites where, if threshold is reached, the impulse is generated.

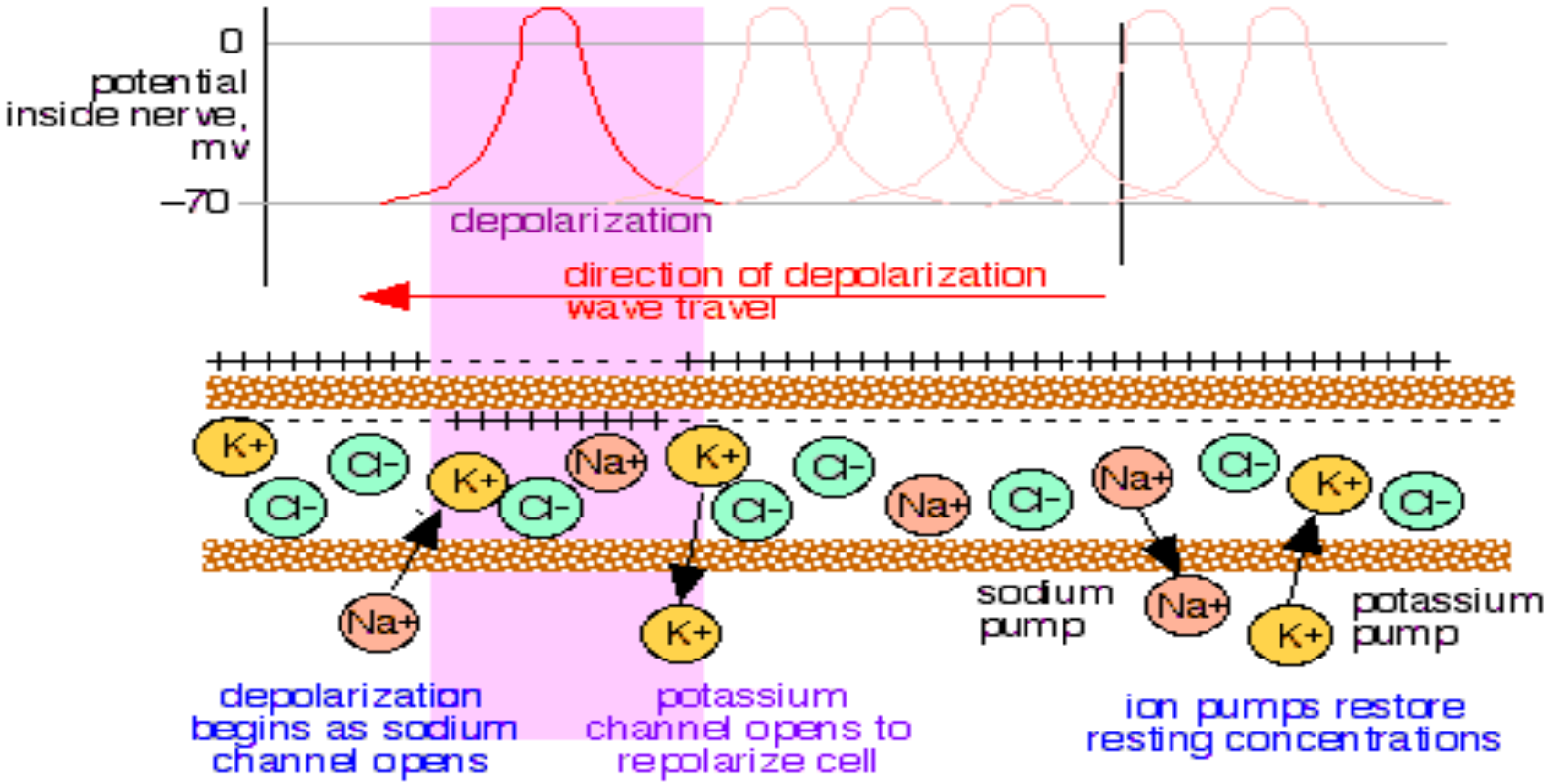
A. In unmyelinated fibres conduction is continuous.

B. In myelinated axons conduction is saltatory – from one node of Ranvier to the next.

C. In dendrites of some neurons are patches of active membrane called ‘hot spots’. They help to conduct the dendritic excitation to the cell body.

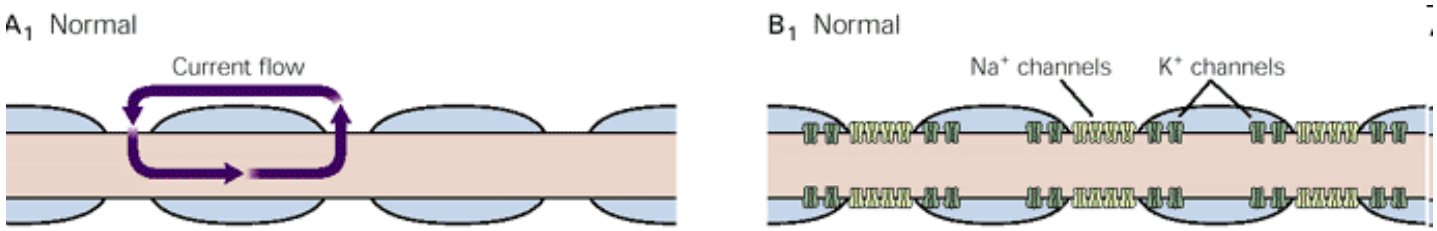
The myelin sheath increases the propagation speed of the nerve impulse and helps in reducing energy expenditure as the area of depolarization and hence the amount of sodium/potassium ions that need to be pumped to bring the concentrations back to normal, is decreased.

Unidirectional conduction of an action potential



Unidirectional conduction of an action potential is due to transient inactivation of voltage-gated Na^+ channels, which remain inactive for several milliseconds after opening. Reopening of Na^+ channels "behind" the action potential is also prevented by the membrane hyperpolarization that results from opening of voltage-gated K^+ channels.

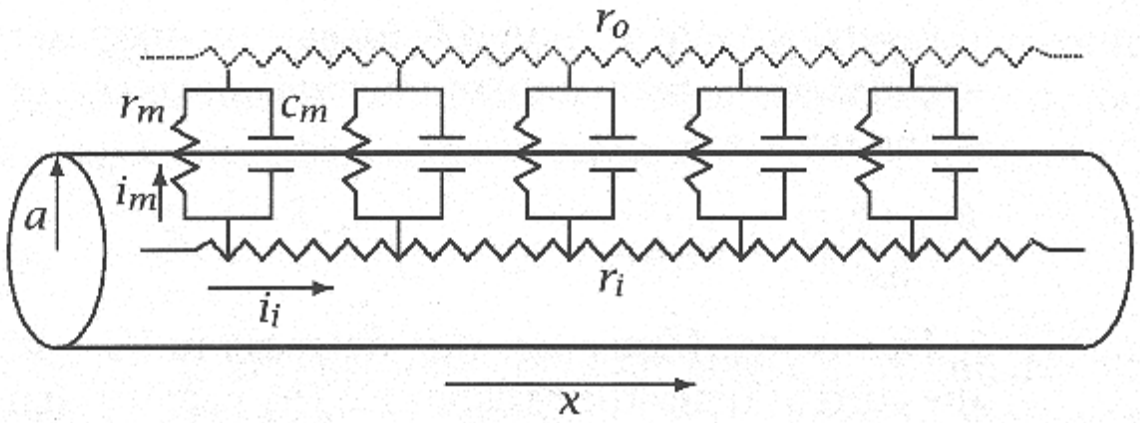
Channels distribution



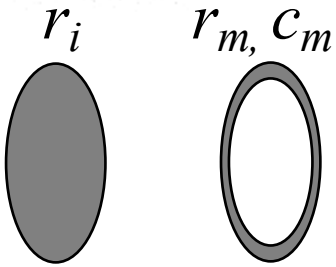
Sodium channels are dense at the node of Ranvier but sparse or absent in the internodal regions of the axon membrane. The K+ channels are located beneath the myelin sheath in internodal regions. There are about 700 000 sodium channels per node, i.e., 12,000 per um^2 of nodal membrane. Internodal membrane can have no more than about 25 channels per um^2.

Propagation of action potentials - cable theory

To describe action potential propagation, it is necessary to derive the cable equation that illustrates how ions diffuse along the axons. In this respect the most useful geometrical structure is a cylinder. The parameters that are defined only for a cylinder are designated by small letters (r_i, r_m, c_m) while parameters that are independent of any specific geometry will by designated by capital letters (R_i, R_m, C_m).



The definitions for the cylinder-dependent parameters are as follows:
r_i – axial resistance (Ω/cm)
r_m – membrane resistance (Ωcm)
c_m – membrane capacitance (F/cm)



r_i corresponds to an infinitely thin disk of the cytoplasm with the same radius as the inside of the cylinder. r_m and c_m correspond to an infinitely thin ring of membrane, with the same radius as the cylinder. Extracellular resistance $r_0 = 0$.

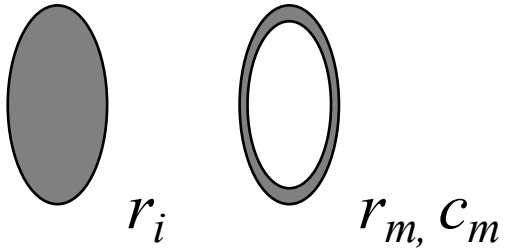
Propagation of action potentials - cable theory

The definitions for the membrane parameters independent of geometry are as follows:

R_i – specific intercelluar resistivity (Ωcm) (resistance across a unit cube of intracellular medium)
R_m – specific membrane resistivity (Ωcm^2) (resistance across a unit area of the membrane)
C_m – specific membrane capacitance (F/cm^2) (capacitance per unit area of the membrane)

The membrane parameters are related to the cable specific parameters as follows:

$$r_i = R_i / \pi a^2$$
$$r_m = R_m / 2\pi a$$
$$c_m = C_m 2\pi a$$



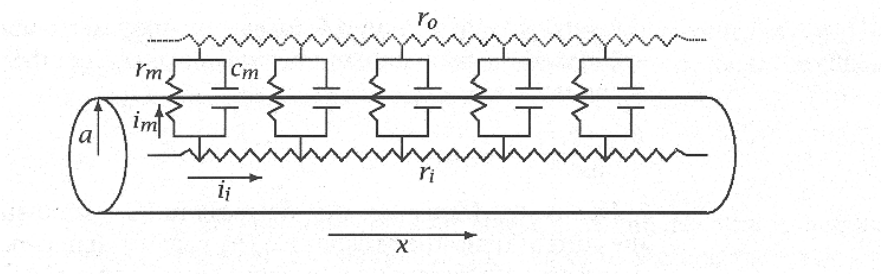
Total values of resistances and conductance (for a cable of length l)

$R_i^{total} = l r_i$ adding resistors in series

$R_m^{total} = r_m / l$ adding resistors in parallel

$C_m^{total} = l c_m$ adding capacitors in parallel

Cable equations of action potential propagation



The decrease in V_m with distance is described by Ohm's law:

$$\frac{\partial V_m(x,t)}{\partial x} = -r_i i_i$$

The decrease in i_i with distance is equal to the current flowing across the membrane

$$\frac{\partial i_i}{\partial x} = -i_m$$

We obtain:

$$\frac{\partial^2 V_m(x,t)}{\partial x^2} = -r_i \frac{\partial i_i}{\partial x} = r_i i_m$$

$$\frac{1}{r_i}\frac{\partial^2 V_m(x,t)}{\partial x^2} = i_m$$

The membrane current I_m (uniform across the membranne) is given by:

$$\frac{\pi a^2}{R_i}\frac{\partial^2 V}{\partial x^2} = I_m 2\pi a$$

$$\frac{a}{2R_i}\frac{\partial^2 V}{\partial x^2} = I_m = C_m \frac{\partial V}{\partial t} + I_K + I_{Na} + I_L$$

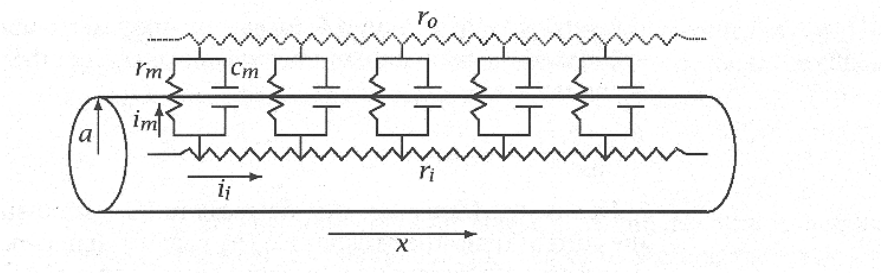
Action potentials propagate with a constant speed, so one can use the wave equation:

$$\frac{\partial^2 V(x,t)}{\partial x^2} = \frac{1}{\theta^2}\frac{\partial^2 V(x,t)}{\partial t^2}$$

where,

θ - conduction velocity (m/s)

Cable equations of action potential propagation



$$\frac{a}{2R_i\theta^2}\frac{d^2V}{dt^2} = C_m\frac{dV}{dt} + I_K + I_{Na} + I_L$$

From this wave equation, one can obtain:

$$\theta = \sqrt{Ka/2R_iC_m} \propto \sqrt{a}$$

K = 10.47 m/s – estimated experimentally

θ= 18.8 m/s

θ_{exp} = 21.2 m/s

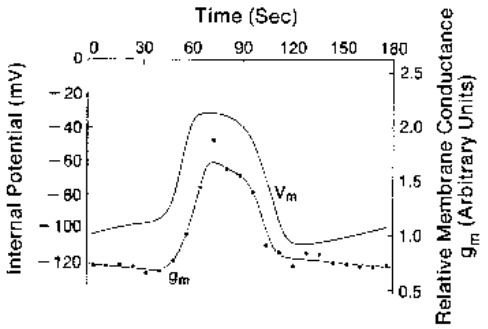
The Hodgkin and Huxley equations therefore give a very good fit to the experimental data

Two myths

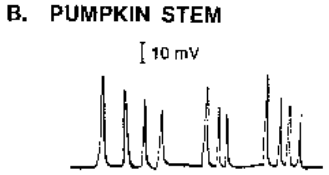
Neuron ⟷ Electrical impulses

Electrical impulses ⟷ Communication

komórka grzyba



pień dyni



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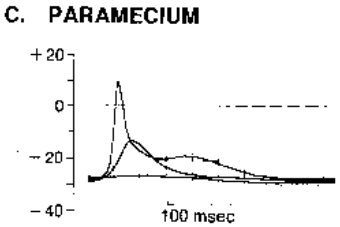

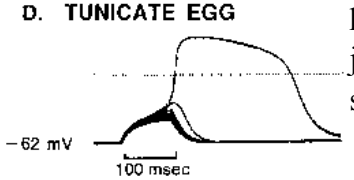

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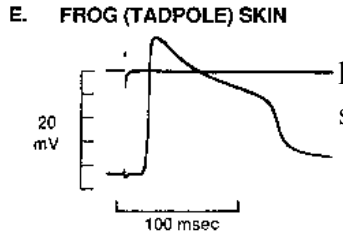

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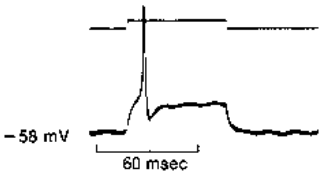
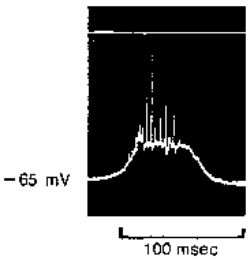


komórka przysadki mógowej szczura



komórka trzustki szczura

Synapse

SIR CHARLES SCOTT SHERRINGTON

So far as our present knowledge goes, we are led to think that the tip of a twig of the arborescence is not continuous with but merely in contact with the substance of the dendrite or cell body on which it impinges. Such a special connection of one nerve cell with another might be called a *synapse*.

Sir Charles Sherrington, 1897, Physiology textbook

<gr. *sýnapsis* to clasp, connect or join>

Interneuronal relations

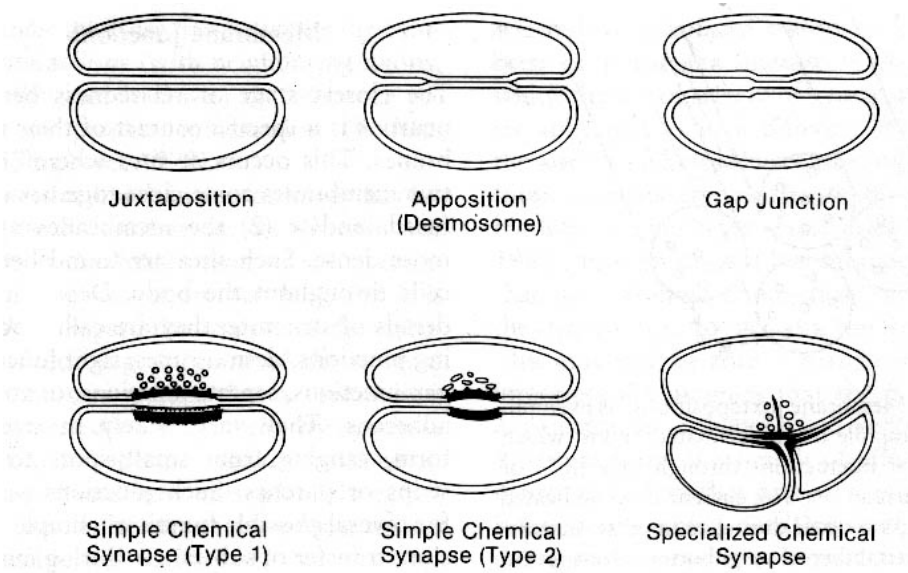
Means of communication in the nervous system:

Volume transmission - actions of neurotransmitters or neuropeptides at a distance, well beyond their release sites from cells or synapses

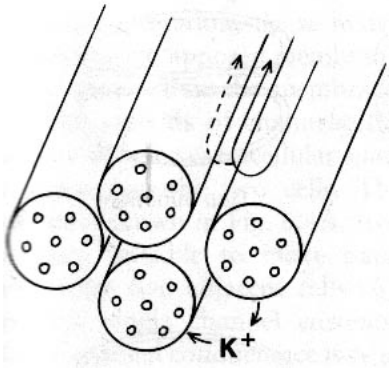
Membrane juxtapositions – the membranes of two neruons are situated close together (~ 20 nm)

Gap junctions – the membranes of two neruons are separated by a gap of 2-4 nm

Chemical synapses – the most complicated and most characteristic.



Types of junctions between nerve cells

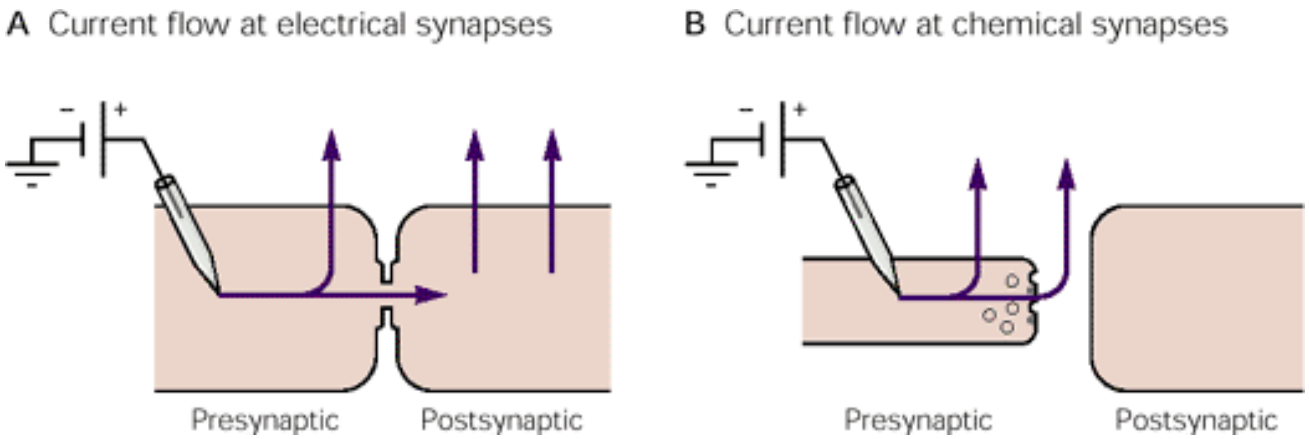


An example of membrane juxtapositions in a bundle of unmyelinated axons, which provide for interactions through ions (K+) or electric current (--).

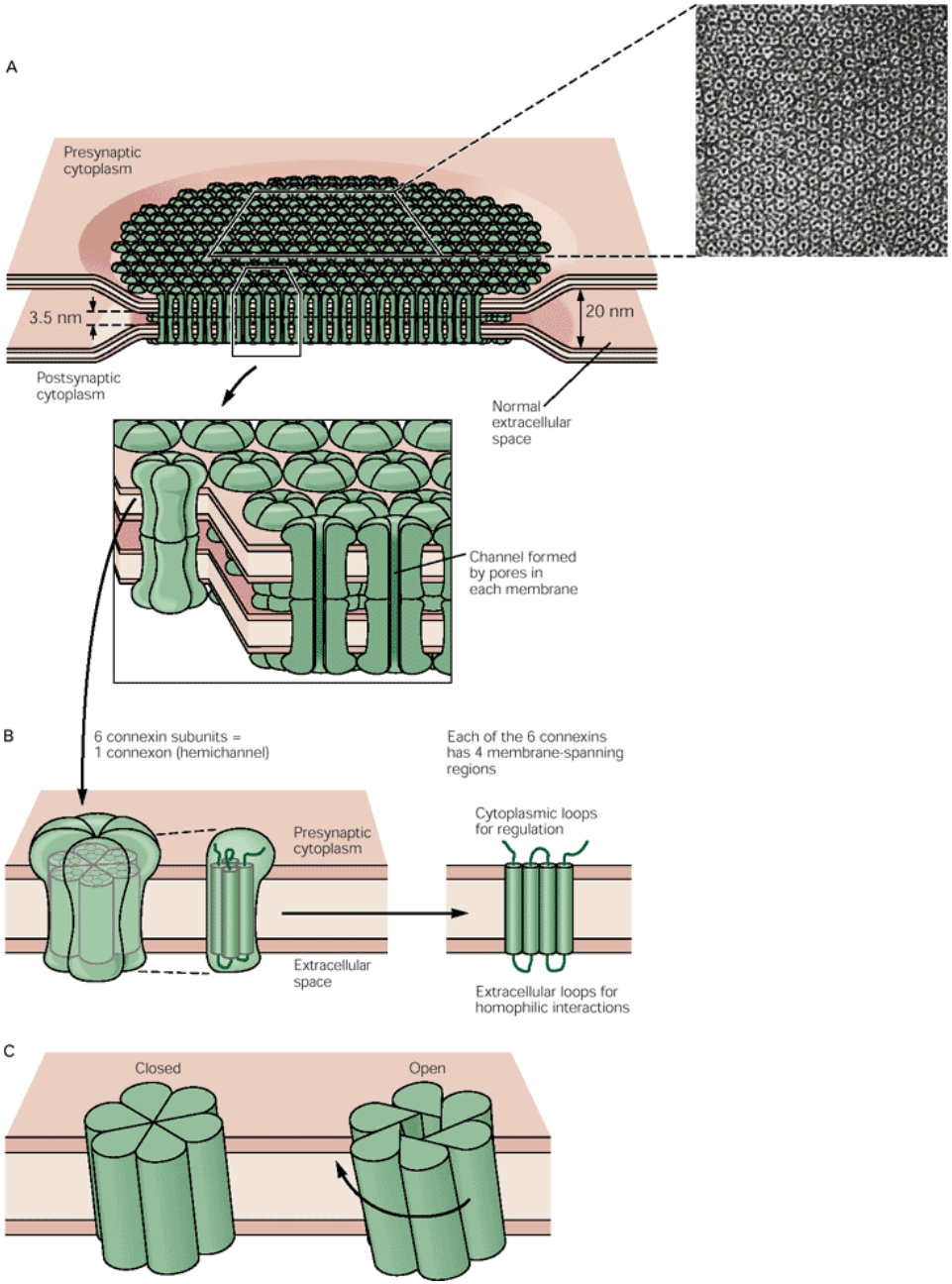
Electrical and Chemical Synapses

Distinguishing Properties of Electrical and Chemical Synapses

Type of synapse	Distance between pre- and postsynaptic cell membranes	Cytoplasmic continuity between pre- and postsynaptic cells	Ultrastructural components	Agent of transmission	Synaptic delay	Direction of transmission
Electrical	3.5 nm	Yes	Gap-junction channels	Ion current	Virtually absent	Usually bidirectional
Chemical	20-40 nm	No	Presynaptic vesicles and active zones; postsynaptic receptors	Chemical transmitter	Significant: at least 0.3 ms, usually 1-5 ms or longer	Unidirectional



Electrical Synapses



A. At electrical synapses two cells are structurally connected by gap-junction channels. A gap-junction channel is actually a pair of hemichannels, one in each apposite cell, that match up in the gap junction through homophilic interactions. The channel thus connects the cytoplasm of the two cells and provides a direct means of ion flow between the cells. This bridging of the cells is facilitated by a narrowing of the normal intercellular space (20 nm) to only 3.5 nm at the gap junction

Electron micrograph: The array of channels shown here was isolated from the membrane of a rat liver. Each channel appears hexagonal in outline. Magnification × 307,800.

B. Each hemichannel, or connexon, is made up of six identical protein subunits called connexins.

C. The connexins are arranged in such a way that a pore is formed in the center of the structure. The pore is opened when the subunits rotate about 0.9 nm at the cytoplasmic base in a clockwise direction. Gap junctions in different tissues are sensitive to different modulatory factors that control their opening and closing. However, most gap-junction channels close in response to lowered cytoplasmic pH or elevated cytoplasmic Ca2+.

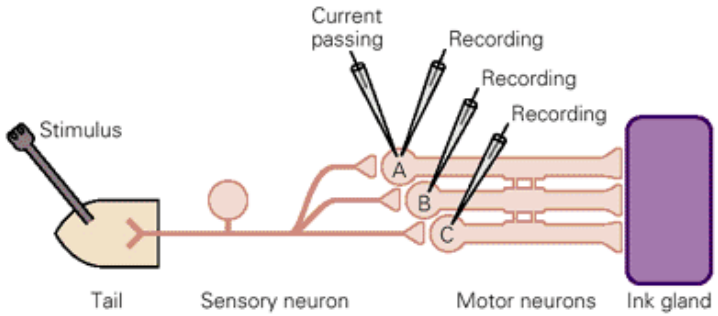
Main characteristics of electical transmission:
- high speed
- high fidelity
- bidirectional

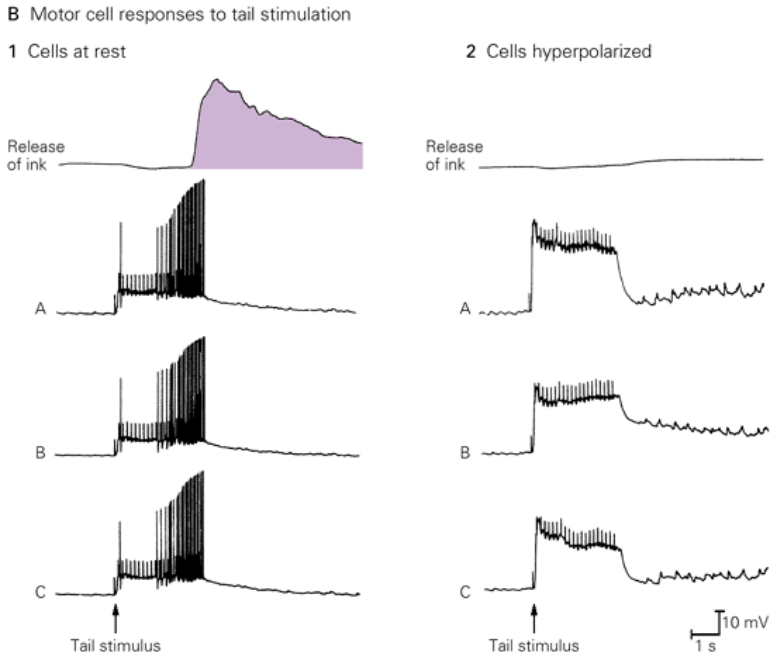
Functions:
- extremely rapid transmission (e.g. tail-flip response)
- synchronization of large group of neurons
- communication in glial cells

Electrical synapses in Aplysia

E. Kandel with Aplysia

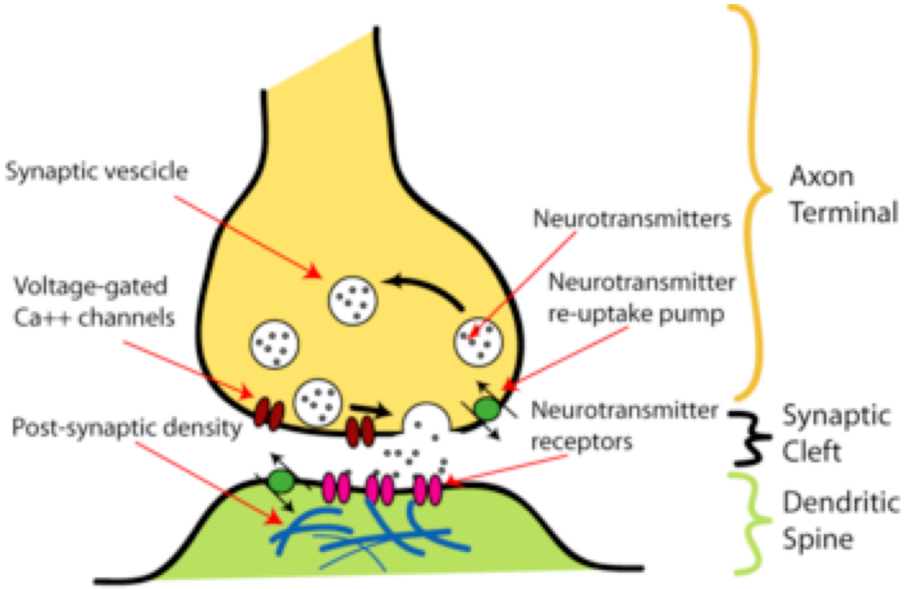
A Neural circuit of the inking response





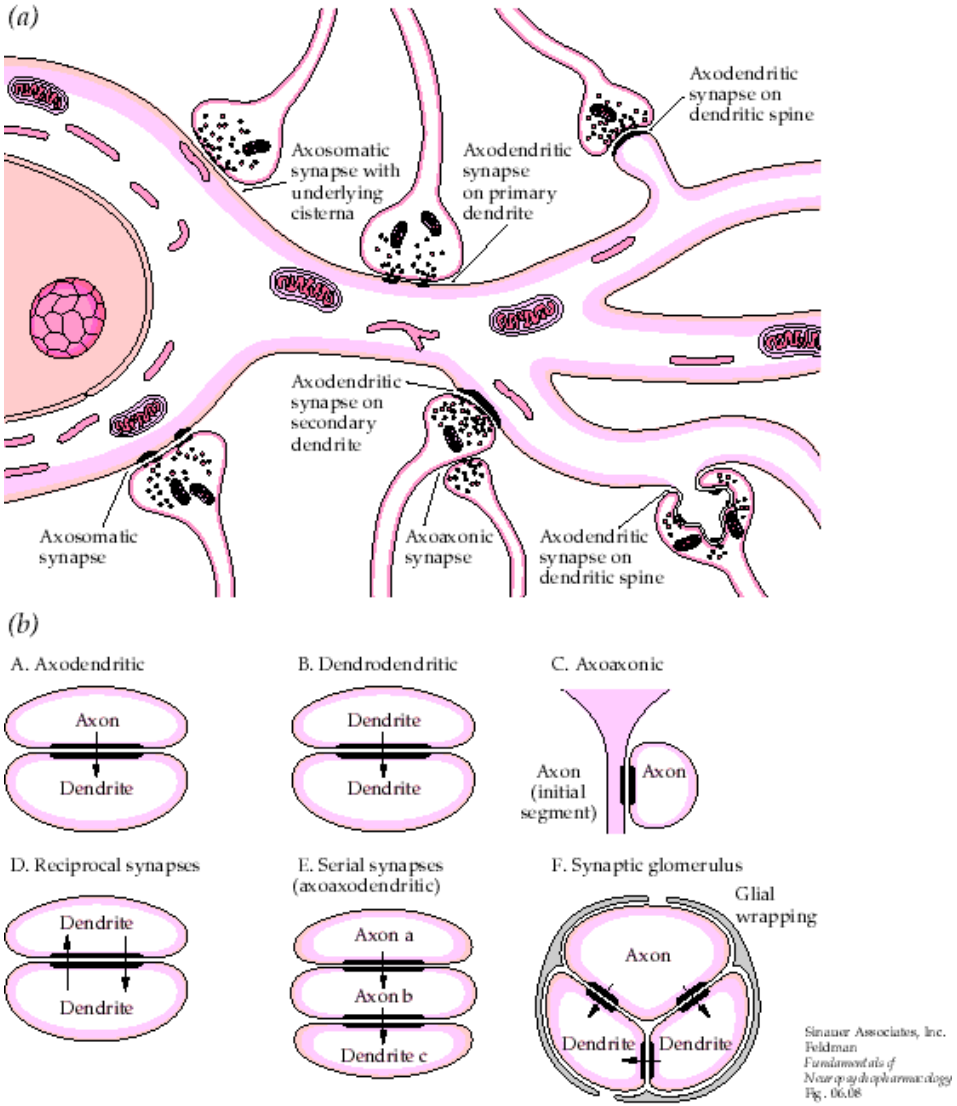
A train of stimuli applied to the tail produces a synchronized discharge in all three motor neurons. **1.** When the motor neurons are at rest the stimulus triggers a train of identical action potentials in all three cells resulting in the release of ink. **2.** When the cells are hyperpolarized the stimulus cannot trigger action potentials. Under these conditions the inking response is blocked.

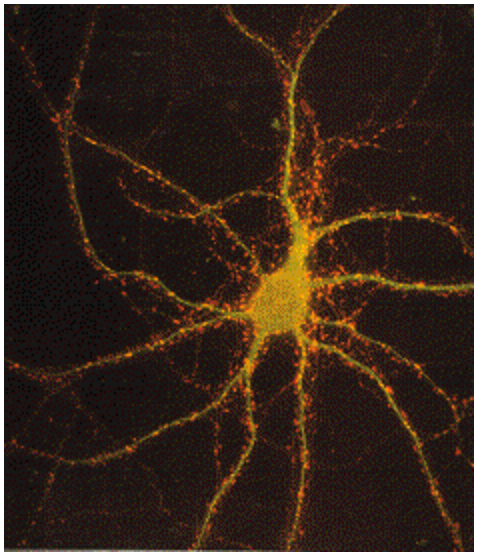
Chemical synapse



1. Action potential in nerve, depolarization of the terminal
2. Activation of voltage-gated Ca^{2+} channels
3. Fusion of vesicle to membrane
4. Release of neurotransmitter (exocytosis)
5. Diffusion of neurotransmitter across the synaptic cleft
6. Binding of neurotrasmitter to receptors and gating of ion channels.
7. Recycling of vesicles (endocytosis)
8. Inactivation of neurotransmitter

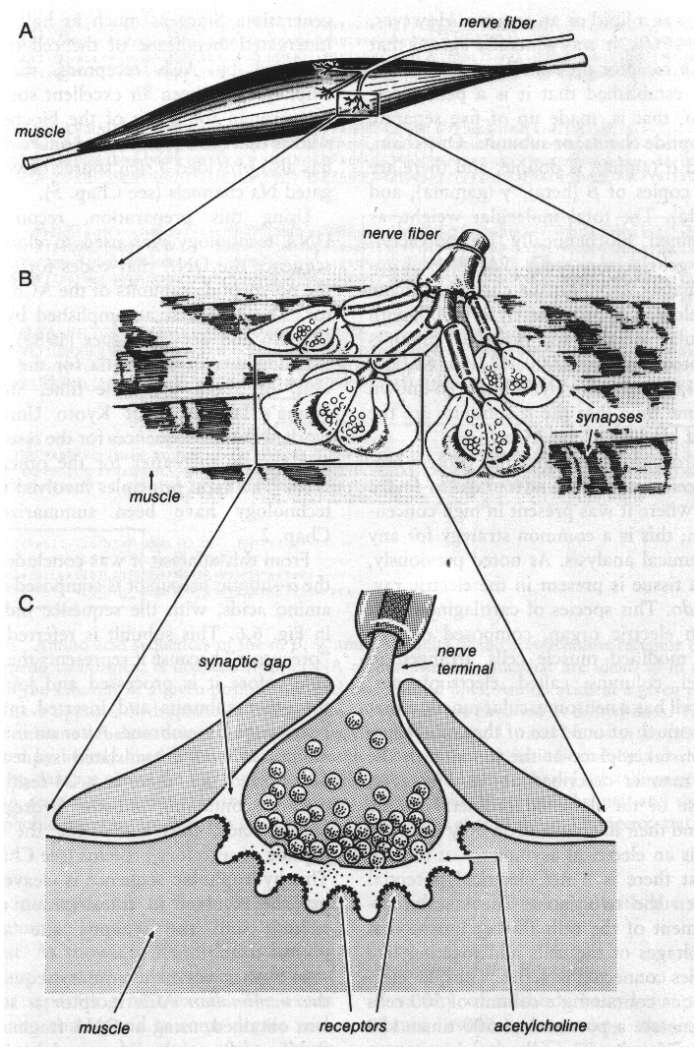
Patterns of synaptic connections



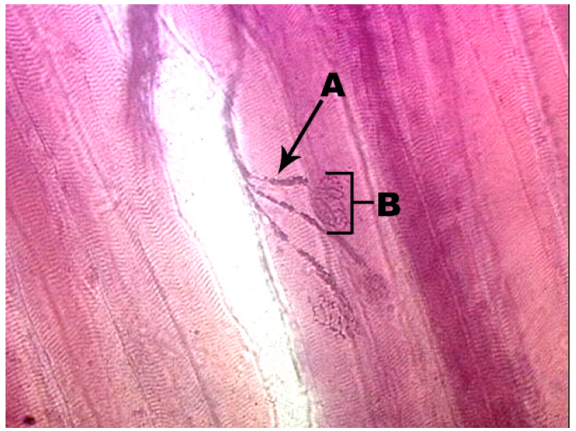


Synapses (orange) in hippocampal cell

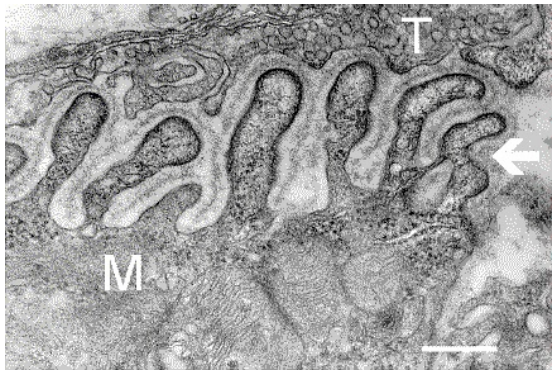
Neuromuscular junction



A muscle is innervated by a motor nerve fiber. The nerve fiber branches to form synaptic junctions with individual nerve fibers. Each junction (endplate) consists of a presynaptic nerve terminal from which acetylocholine is released, synaptic cleft, a postsynaptic area on the muscle containing receptors, and a surrounding envelope of glia.

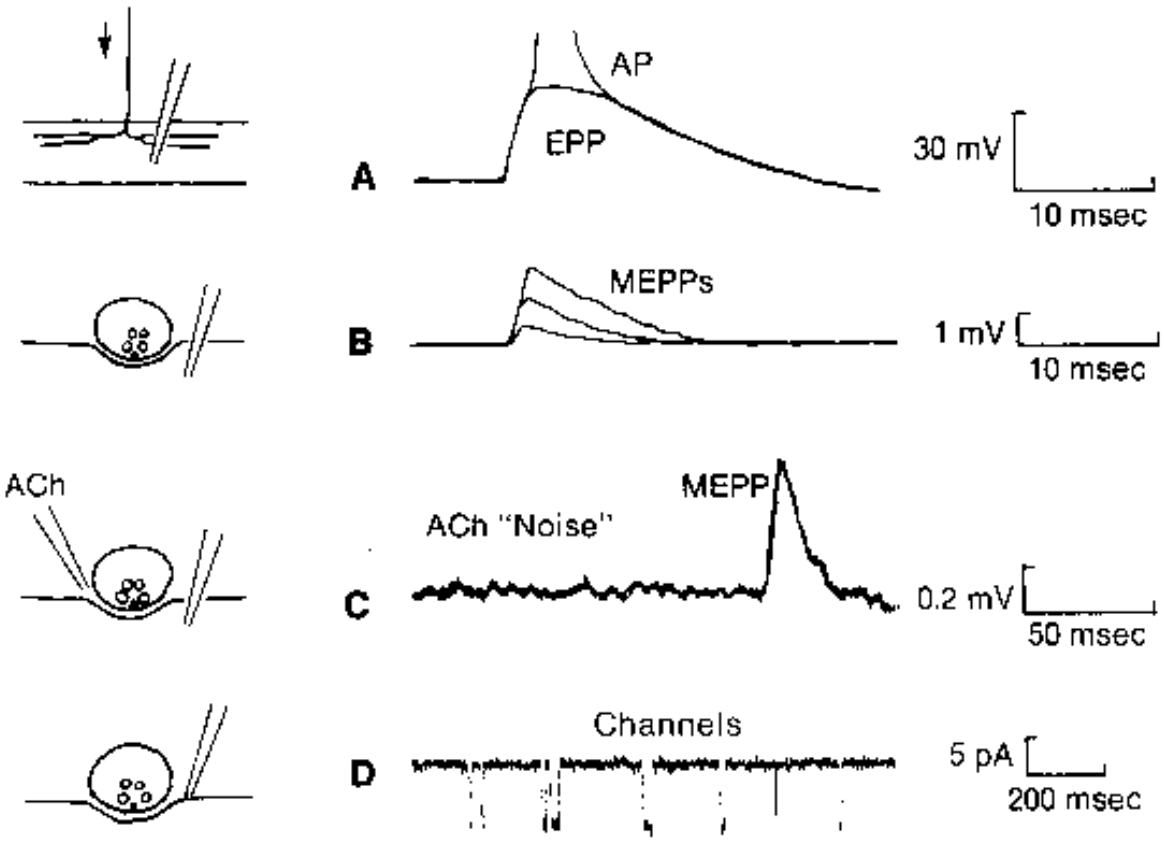


Three neuromuscular junctions magnified 400X. Axon terminal [A] from a neuron is shown terminating into a large synaptic terminal [B] which communicates with a single skeletal muscle fiber.



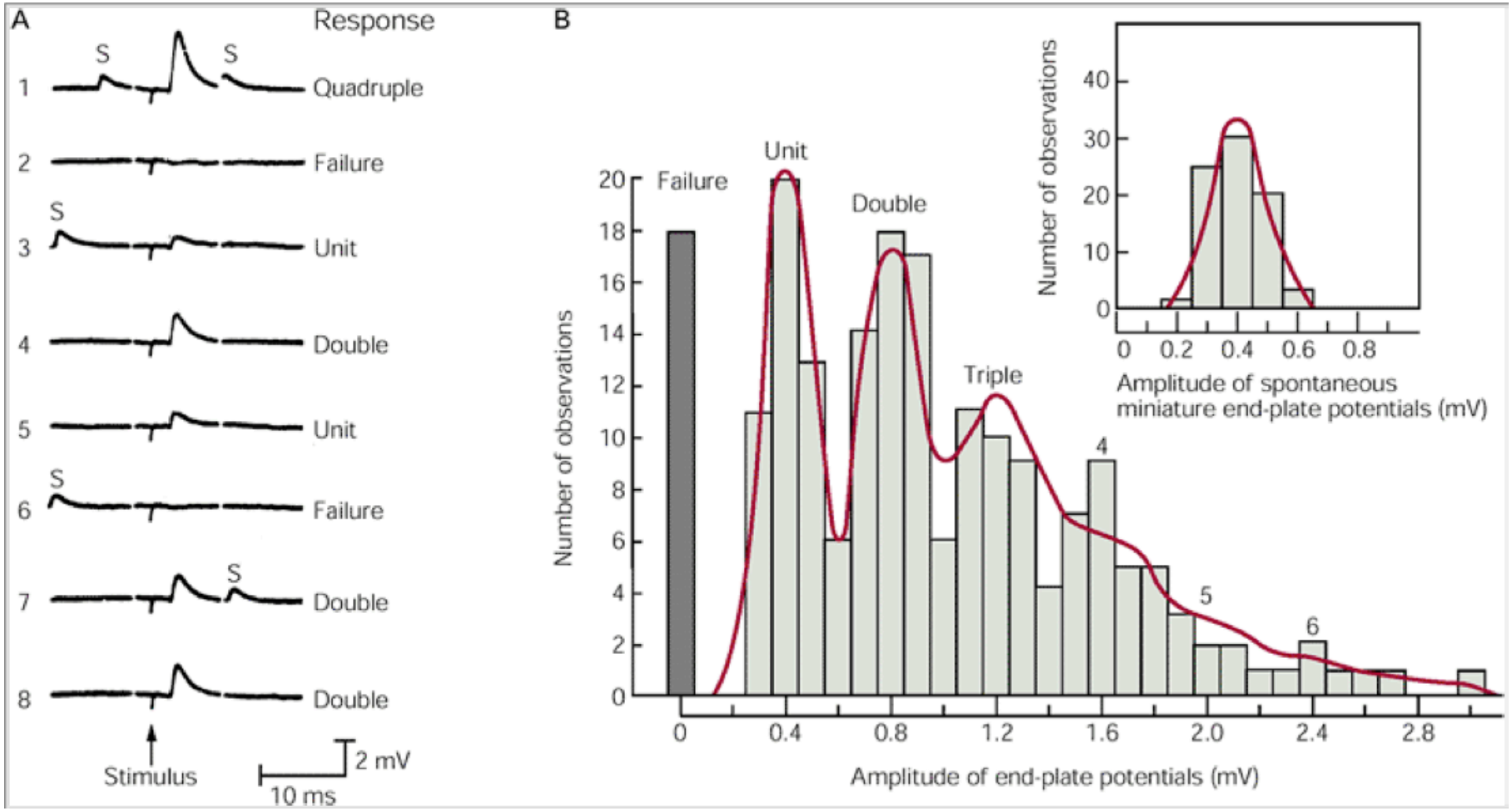
Electron microscope autoradiograph of the neuromuscular junction. T – axon terminal, M – muscle fiber. Scale 0.3 mm.

Neuromuscular junction – endplate potentials



A. Intracellular recording of endplate potential (EPP) giving rise to an action potential (AP) in the muscle cell; experimental setup shown at left. B. High-gain recording showing summation of miniature endplate potentials (MEPPs). A single MEPP is due to a release of single quantum of ACh (~10000 molecules) (one quantum ~ one vesicle). Quanta released in synchrony by the impulse lead to summation of MEPPs and give rise to a large potential EPP. C. Very high gain recording showing noise induced by ionophopresis (using a small electric charge to deliver a chemical through the membrane) of ACh. D. Patch – clamp recording showing currents passing through single AChR channels.

Neuromuscular junction – endplate potentials



A. Intracellular recordings from a muscle fiber at the endplate (S denotes spontaneous MEPPs). B. The distribution of responses. The peaks in the histogram occur at amplitudes that are integral multiples of the amplitude of the unit potential (0.4 mV). This unit response is the same amplitude as the spontaneous miniature end-plate potentials (inset).

Quantal hypothesis (del Castillo, Katz, Martin)

Neurotransmitter is released in quanta. Quantal release is a statistical, probabilistic, not a deterministic process.

$$m = np$$

m – number of quanta released

n – number of possible quanta

p – average probability of release

$n \sim 1000$

$m \sim 100\text{-}200$

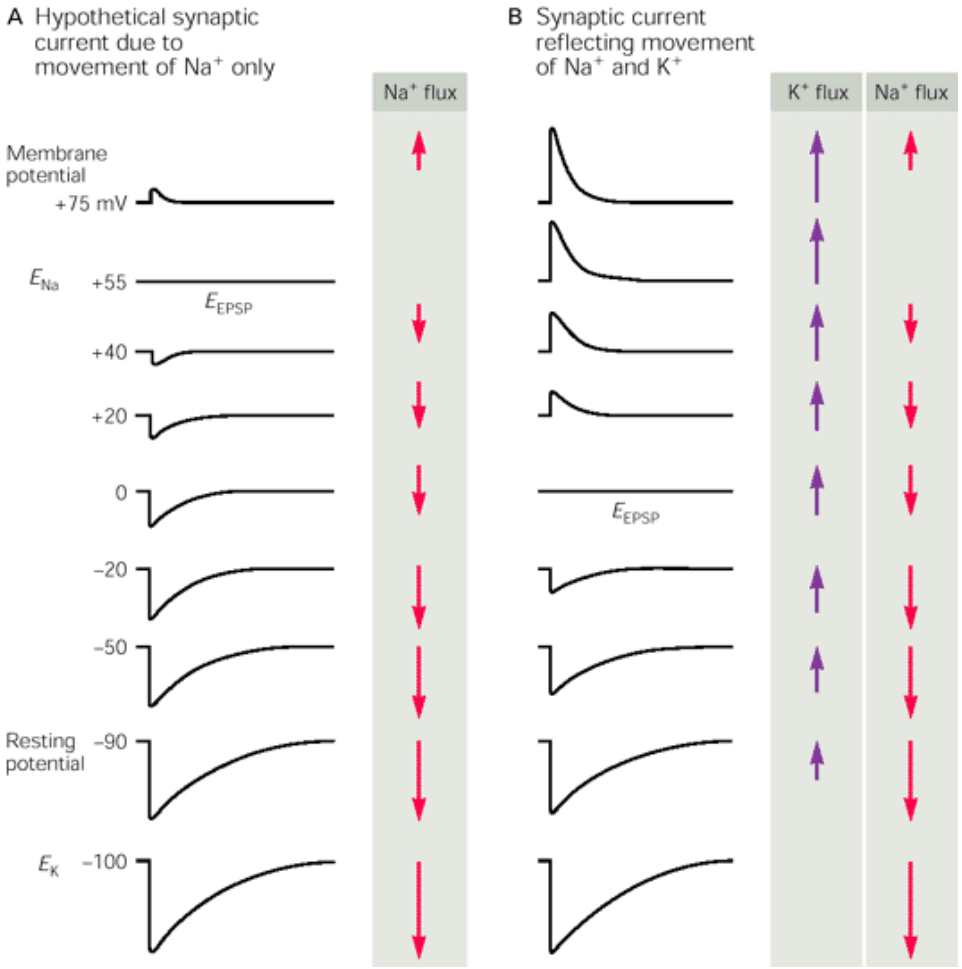
$p \sim 0.1 - 0.2$

The release of neurotransmitter in quanta applies to most of chemical synapses. The release process (probability) is controlled by the amount of depolarization of the nerve terminal membrane, which influences calcium level. The greater the Ca2+ influx into the terminal, the larger the number of quanta released.

The Ion Channel at the End-Plate Is Permeable to Both Sodium and Potassium

The end-plate current is given by: $I = g(V - E_{EPSP})$

I - the end-plate current, g – the conductance of the ACh-gated channels, V – the membrane potential, E_{EPSP} – the chemical driving force, or battery.

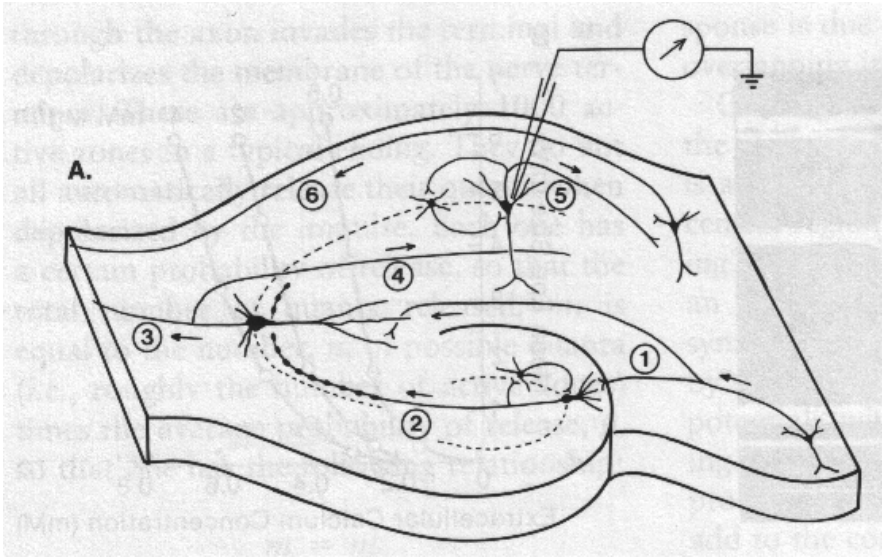


The ionic currents responsible for the end-plate potential can be determined by measuring the reversal potential of the end-plate current. The voltage of the muscle membrane is clamped at different potentials, and the synaptic current is measured when the nerve is stimulated.

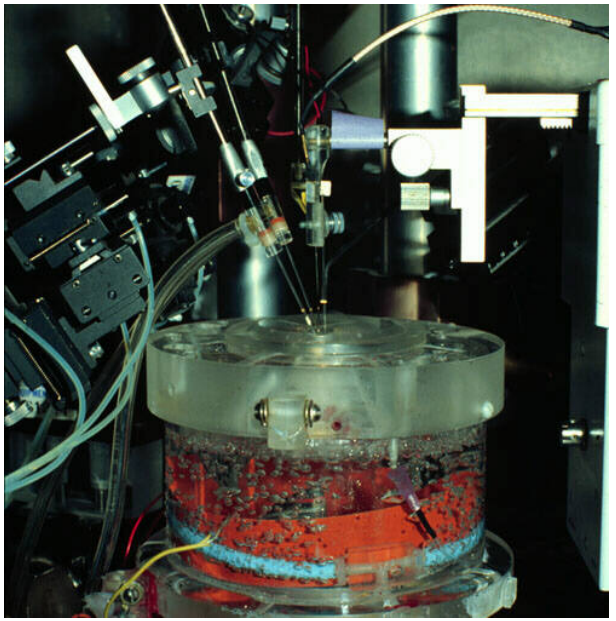
A. If Na+ flux alone were responsible for the end-plate current, the reversal potential would occur at +55 mV, the equilibrium potential for Na+ (E_{Na}). The arrow next to each current record reflects the magnitude of the net Na+ flux at that membrane potential.

B. The end-plate current actually reverses at 0 mV because the ion channel is permeable to both Na+ and K+, which are able to move into and out of the cell simultaneously. The net current is the sum of the Na+ and K+ fluxes through the end-plate channels. At the reversal potential (E_{EPSP}) the inward Na+ flux is balanced by an outward K+ flux so that no net current flows.

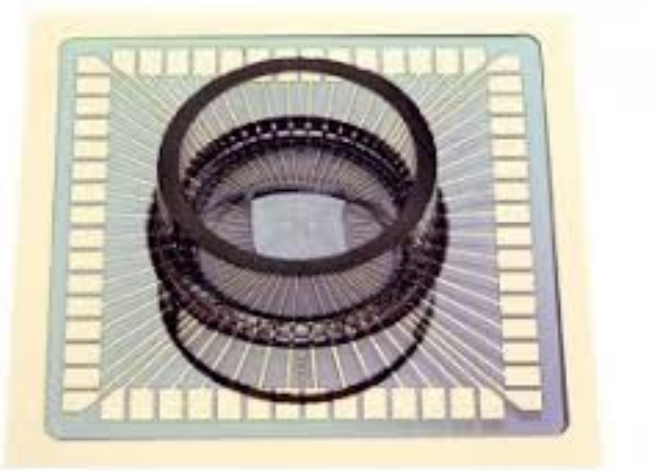
Studying synapses



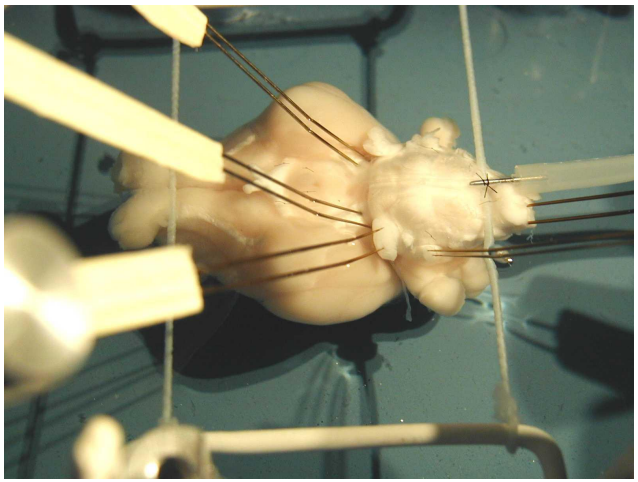
Hippocampal slice



in vitro chamber



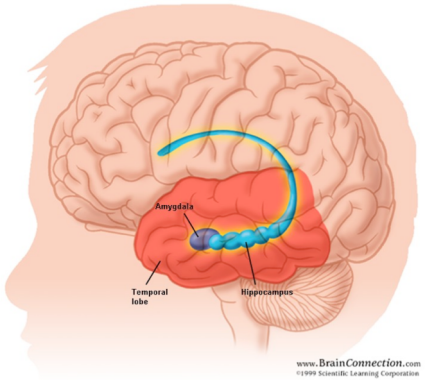
Microelectrode array

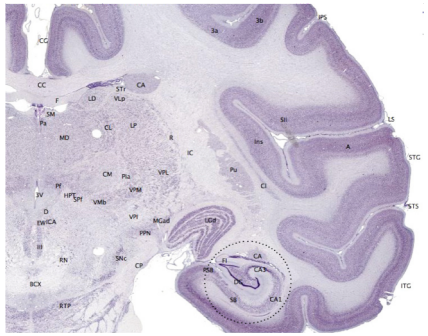


Brain preparation *in toto*

Hippocampus

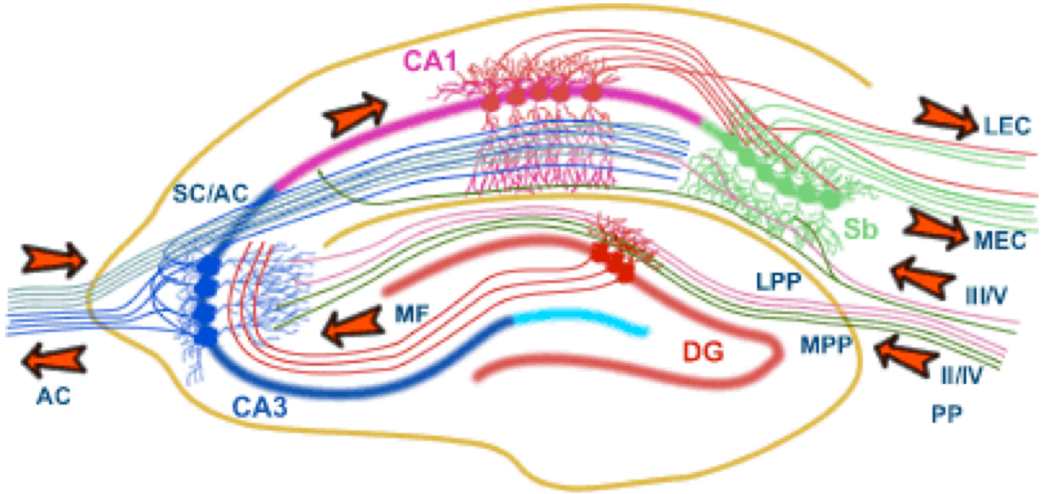
The hippocampus is perhaps the most studied structure in the brain. It is critical to spatial learning and awareness, navigation, episodic/event memory and associational recollection.





The hippocampus is a part of the cerebral cortex, and in primates it is located in the medial temporal lobe, underneath the cortical surface

Sea horse (*Hippocampus*)

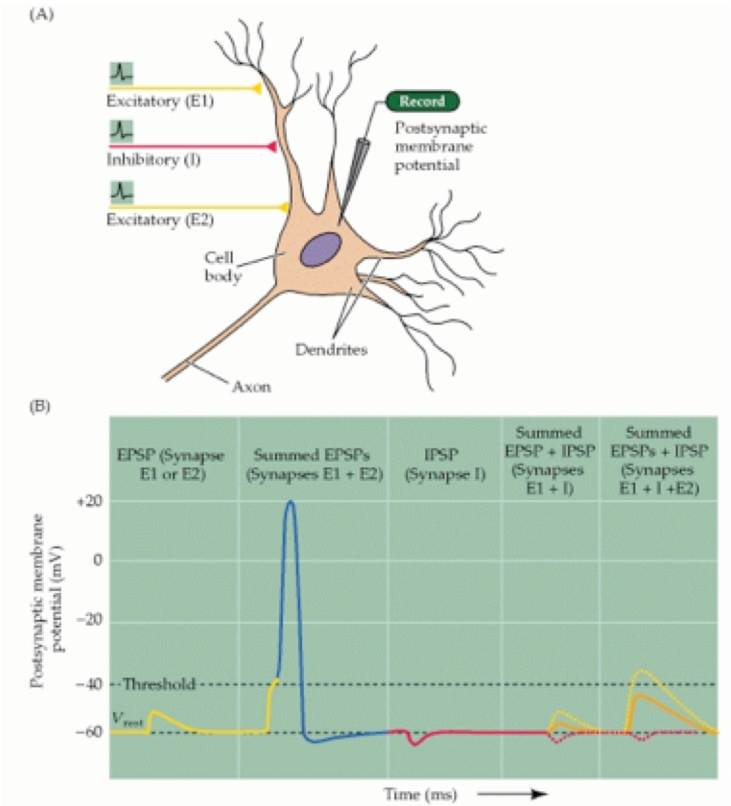


The hippocampal Network: The hippocampus forms a principally uni-directional network, with input from the Entorhinal Cortex (EC, layers II-V) that forms connections with the Dentate Gyrus (DG) and CA3 pyramidal neurons via the Perforant Path (PP - split into lateral and medial). CA3 neurons also receive input from the DG via the Mossy Fibres (MF). They send axons to CA1 pyramidal cells via the Schaffer Collateral Pathway (SC), as well as to CA1 cells in the contralateral hippocampus via the Associational Commisural (AC) Pathway. CA1 neurons also receive inputs directly from the Perforant Path and send axons to the Subiculum (Sb). These neurons in turn send the main hippocampal output back to the EC, forming a loop.

Entorhinal cortex - kora śródwęchowa, Subiculum - podkładka, Dentate gyrus - zakręt zębaty.

Excitatory and inhibitory synaptic potentials

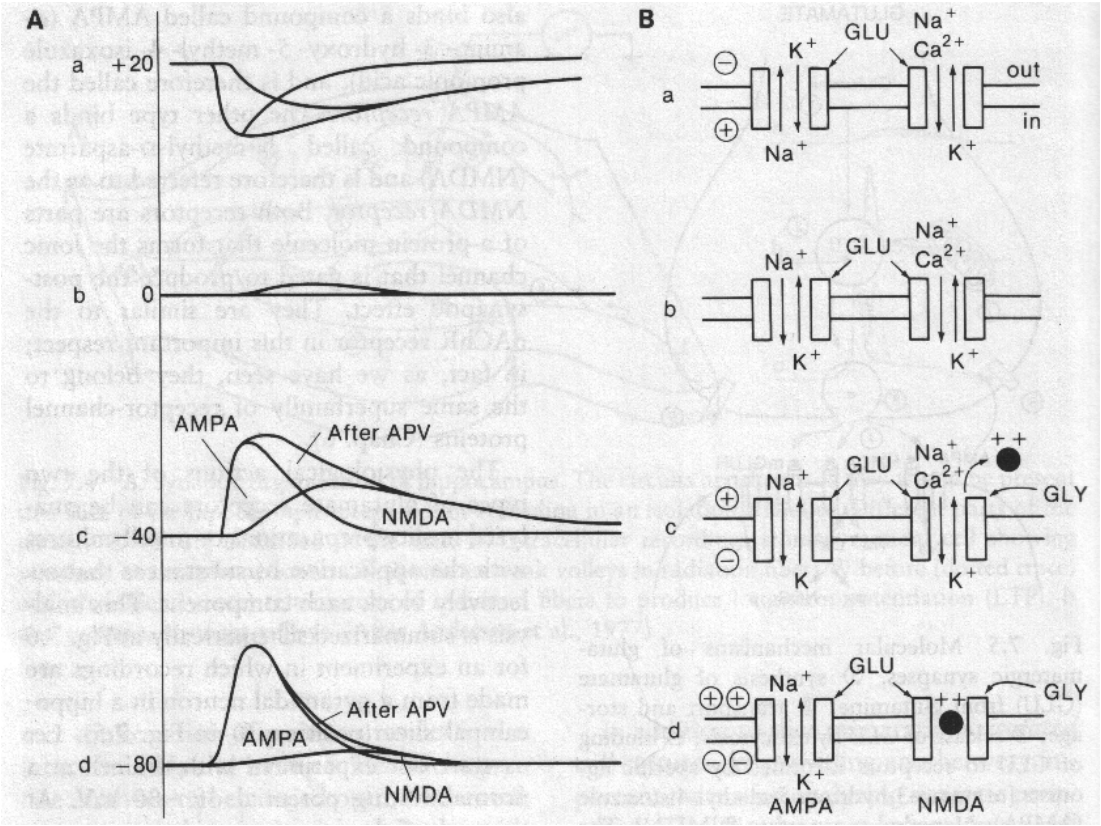
Postsynaptic potentials change the probability that an action potential will be generated. They are called excitatory (or EPSP) if they increase the likelihood of a postsynaptic action potential, and inhibitory (or IPSP) if they decrease this likelihood.



A cell with three synapses – two excitatory (E1, E2) and one inhibitory (I). Activation of E1 or E2 leads to EPSP. Activation of E1+E2 leads to EPSP, which evokes an action potential. Activation of I results in IPSP. Activation of E1+E2+I keeps the neuron below the threshold.

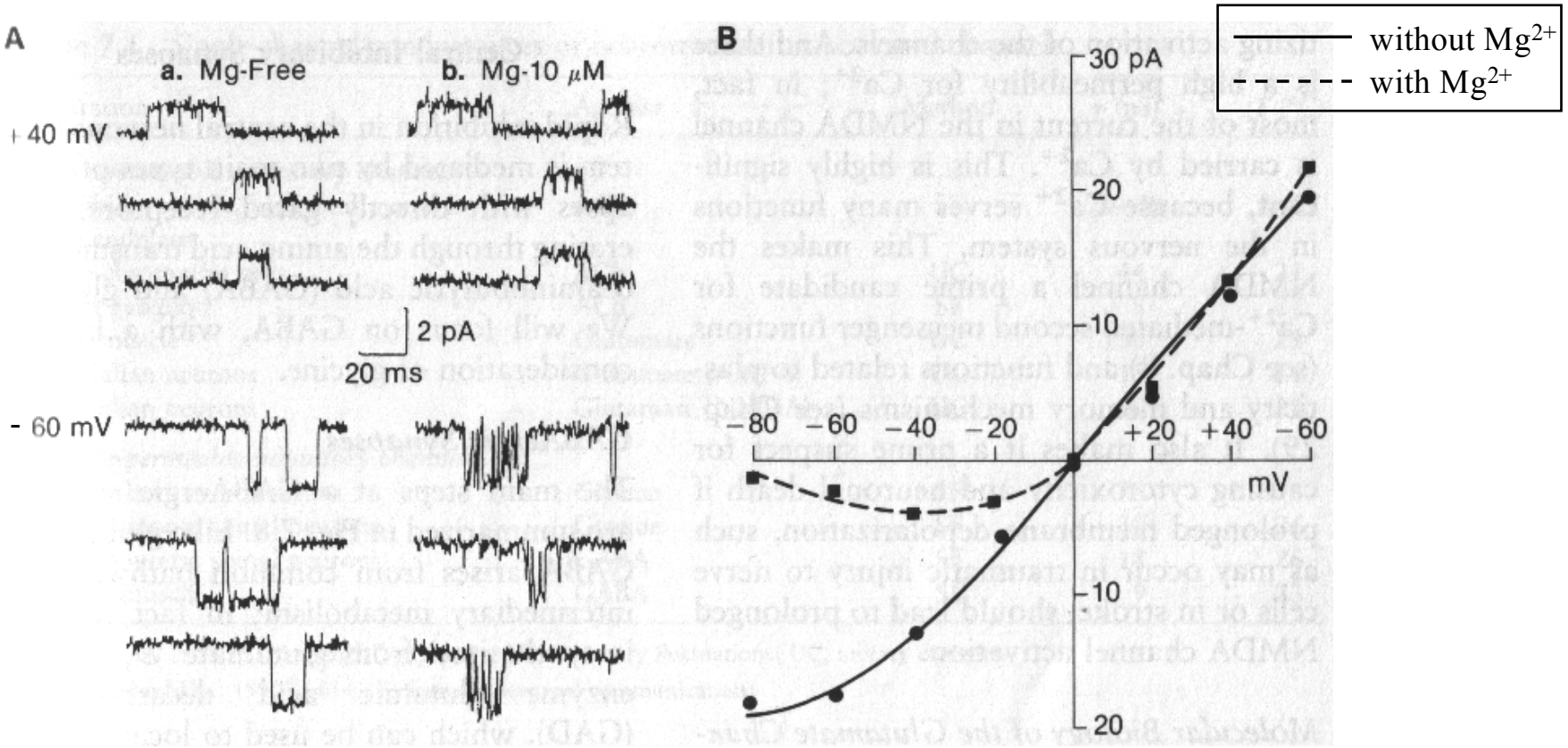
Excitatory synapses

There are two main types of glutamate receptors:
AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
NMDA: N-methyl-D-aspartate
Synaptic current is given by: $I = g(V - E_{EPSP})$



A. Intracellular recordings from a neuron responding to excitatory synaptic input at different holding potentials. The responses are shown before and after exposure to antagonists of the AMPA and NMDA receptors (APV is a NMDA receptor blocker). B. Diagrams showing AMPA and NMDA channels and the current flows through them.

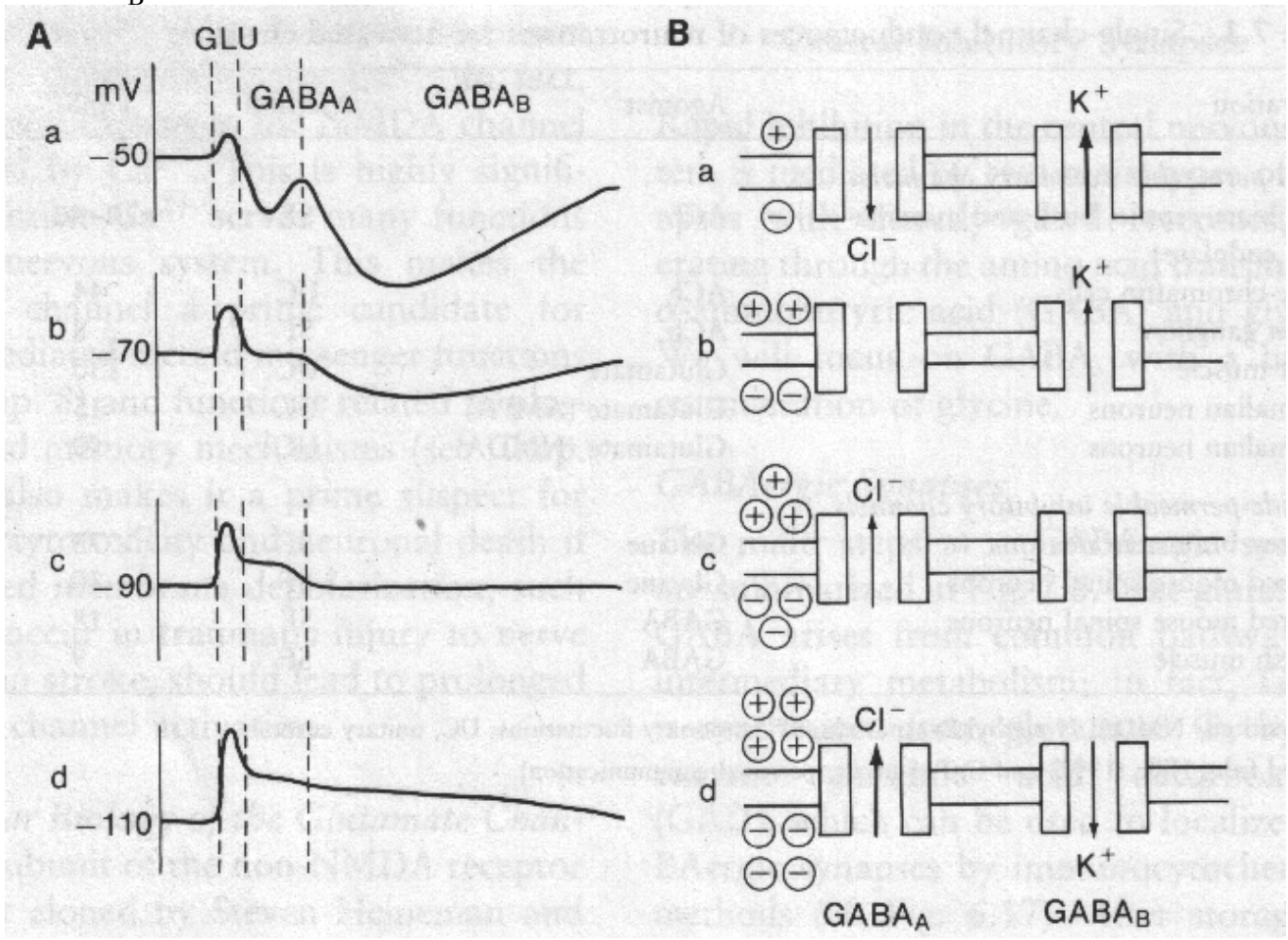
Properties of NMDA receptors



NMDA receptor is voltage dependent due to voltage sensitivity of the Mg+ block.

Inhibitory synapses

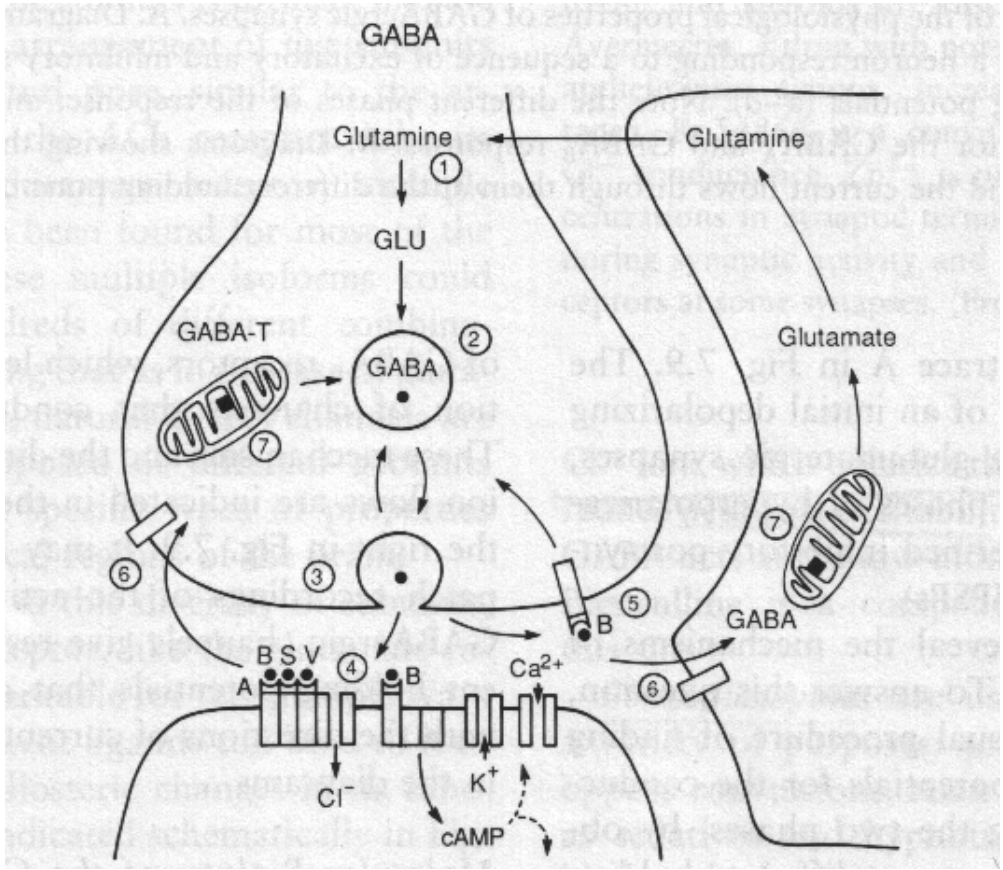
There are two types of GABA (γ-aminobutyric acid) receptors:
$GABA_A$
$GABA_B$



A. Intracellular recordings from a neuron responding to a sequence of excitatory and inhibitory synaptic inputs at different holding potentials. Different reversal potentials for the $GABA_A$ (-70 mV) and $GABA_B$ (-90 mV) suggest involvement of Cl- and K+ ions.

Ionotropic and metabotropic receptors

Ionotropic receptors gate directly ion channels. Metabotropic receptors gate ion channels indirectly through coupling to a G-protein or through second-messanger system activated by G-protein.



$GABA_A$: neurotransmitter -> Cl^- channel opening

$GABA_B$: neurotransmitter -> increased level of cAMP (cyclic adenosine monophosphate) (SM) ->K^+ channel opening

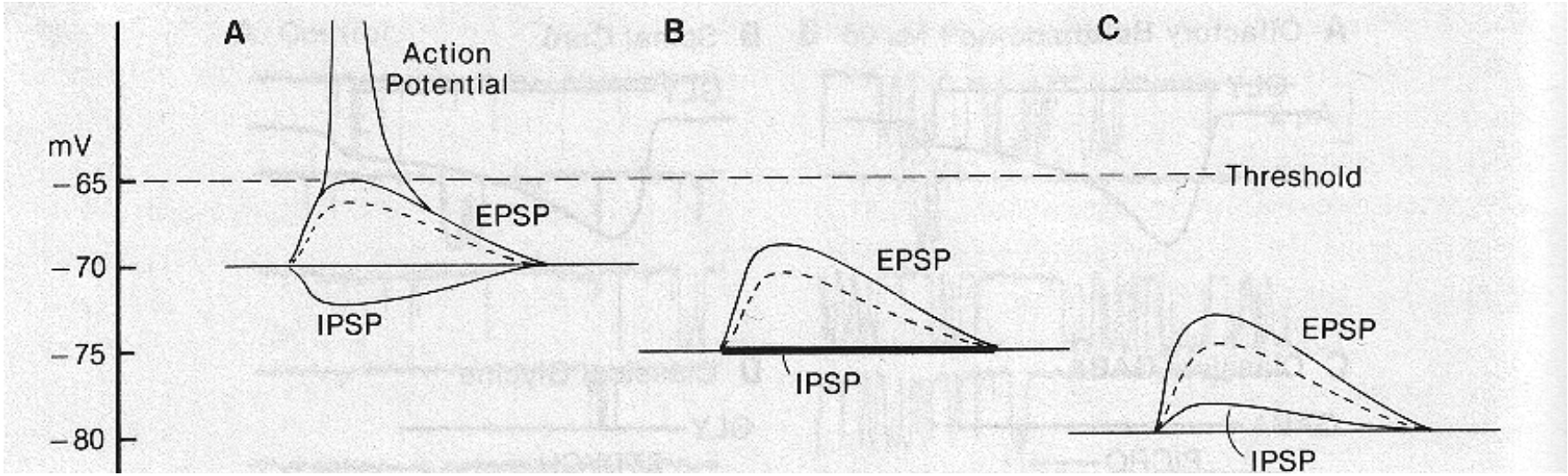
Ionotropic and metabotropic receptors

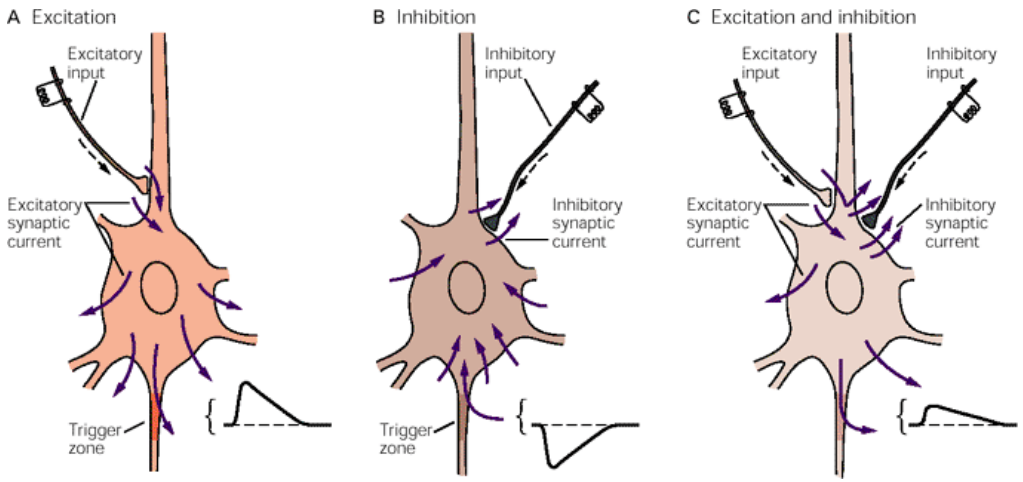
Ionotropic		
Neurotransmitter	Receptor	Ion
Glutamate	AMPA	$Na^+/K^+/Ca^{2+}$ (some)
	Kainate	$Na^+/K^+/Ca^{2+}$ (some)
	NMDA	$Na^+/K^+/Ca^{2+}$
Acetylcholine (ACh)	nicotinic	$Na^+/K^+/Ca^{2+}$ (some)
Serotonin (5-HT)	$5\text{-}HT_3$	Na^+/K^-
ATP	Purine P1	Na^+/K^+
γ-aminobutyric acid (GABA)	A	Cl^-
Glycine		Cl^-

Metabotropic		
Neurotransmitter	Receptor	Ion
Glutamate	Quisqualate	G-coupled ↓ K^+
ACh	muscarinic (M1–5)	G-coupled ↓ K^+ (M-current), ↓ K^+ (AHP) ↑ K^- (Inward rectifier) ↓ Cl^- ↓ Ca^{2+}(N & L), ↑ Ca^{2+}(T)
GABA	B	G-coupled ↑K^+, ↓Ca^{2+}(N)
Norepinephrine (NE) (α, β)	β α α_2	G-coupled ↓ K^- (AHP), ↑ Ca^{2+}(L & N) ↓ Ca^{2+}(N) ↑ K^+
Dopamine (DA)	(D_1, D_2,...)	G-coupled ↓ K^+(AHP)
5-HT	$5\text{-}HT_2$ $5\text{-}HT_{1A}$	G-coupled ↓ K^+ (M-current) ↓ K^- ↑ K^+
Histamine	(H_1,...)	G-coupled ↓ K^+(AHP)
Adenosine	(A_1,...)	G-coupled ↑ K^+, ↓ Ca^{2+}
Opioids (μ, δ, κ)	μ μ κ	G-coupled ↑ K^- (inward rectifier) ↑ K^+ (voltage-dependent) ↓ Ca^{2+}
Substance P		G-coupled ↓ K^+(M-current)
Somatostatin		G-coupled ↑ K^- (M-current)
Bradykinin		G-coupled ↓ K^+(M-current), ↓ K^-(AHP)
VIP		G-coupled
Cholecystokinin		G-coupled
NPY		G-coupled ↓ Ca^{2-}(N)
Neurotensin		G-coupled
TRH		G-coupled
Vasopressin		G-coupled
Oxytocin		G-coupled
CRF		G-coupled
LHRH		G-coupled ↓ K^+(M-current)

The response of ionotropic receptors is fast and shortlasting, the response of metabotropic receptors is slower and has larger duration.

Shunting inhibition



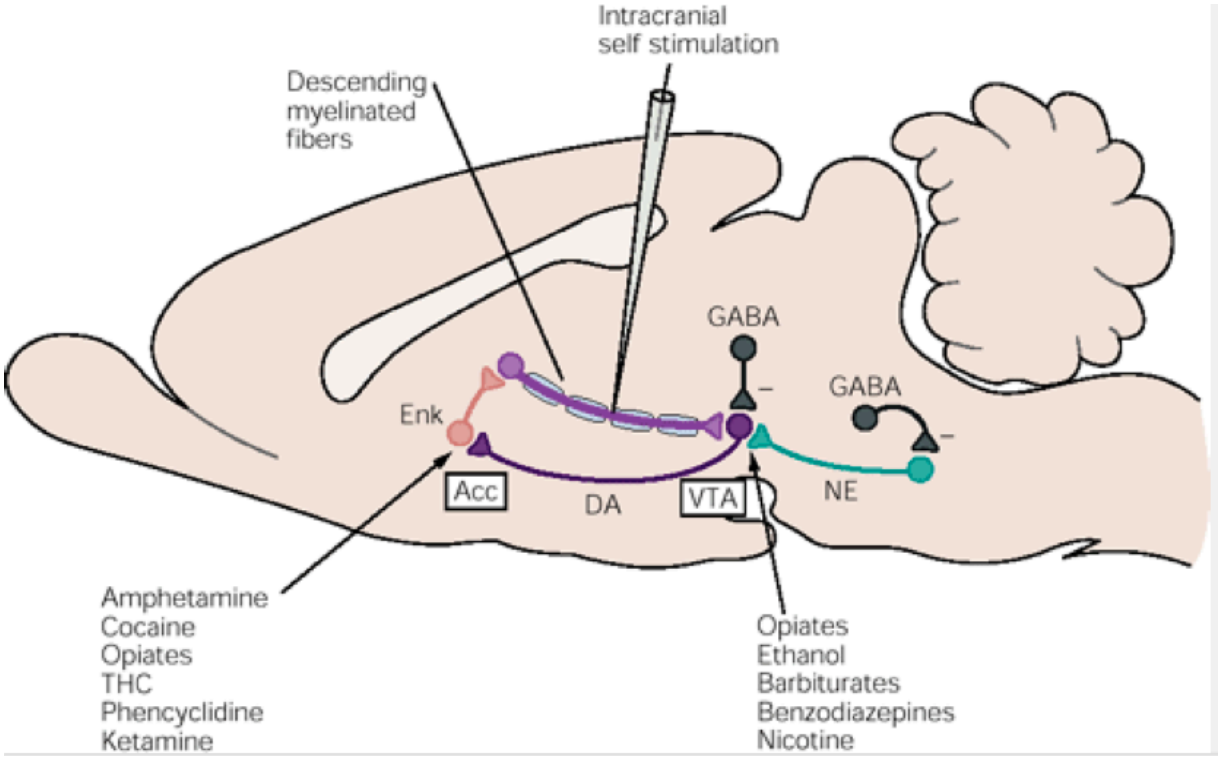


The shunting action of inhibition. When the cell receives both excitatory and inhibitory synaptic current, the channels opened by the inhibitory pathway shunt the excitatory current, thereby reducing the excitatory synaptic potential.

Railroad shunting in Holland

Drugs and neurotransmitters

Various medical (sleeping pils, antidepressants) and recreational drugs interact with neurotransmission. Many addictive drugs increase the level of dopamine released in the brain, by blocking dopamine reuptake (cocaine, amphetamine), by enhancing dopamine release (nicotine) or by inhibition of GABA-ergic neurons that normally suppress dopaminergic neurons (opiates). This results in increased extracellular concentrations of dopamine and increase in dopaminergic neurotransmission.



Brain-reward circuitry in the rat. Acc = nucleus accumbens; DA = dopaminergic fibers; Enk = enkephalin and other opioid- containing neurons; GABA = GABA-ergic inhibitory interneurons; NE = norepinephrine-containing fibers; THC = tetrahydrocannabinol; VTA = ventral tegmental area.