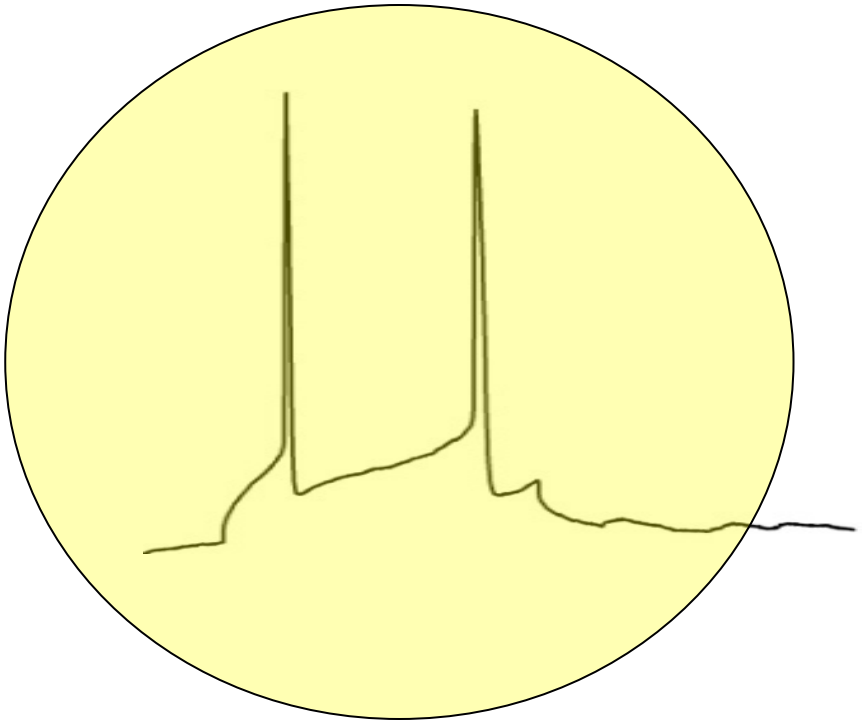
Nervcellsfysiologi

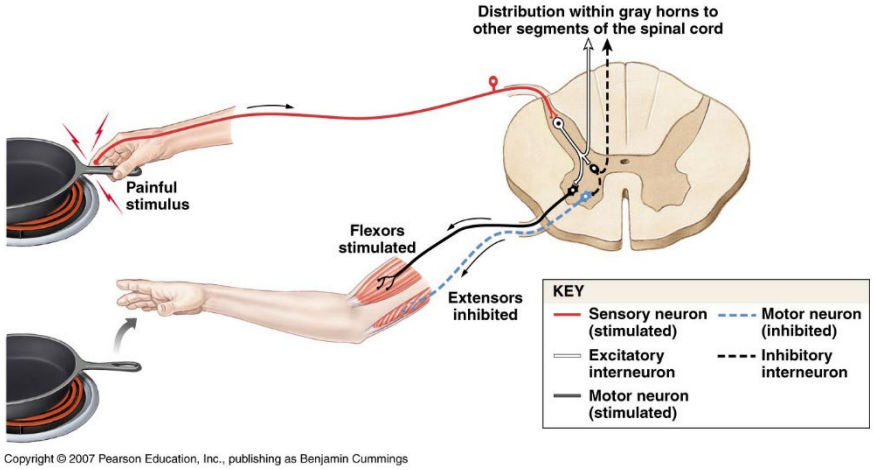


Textbooks:
Bear kap:2-6

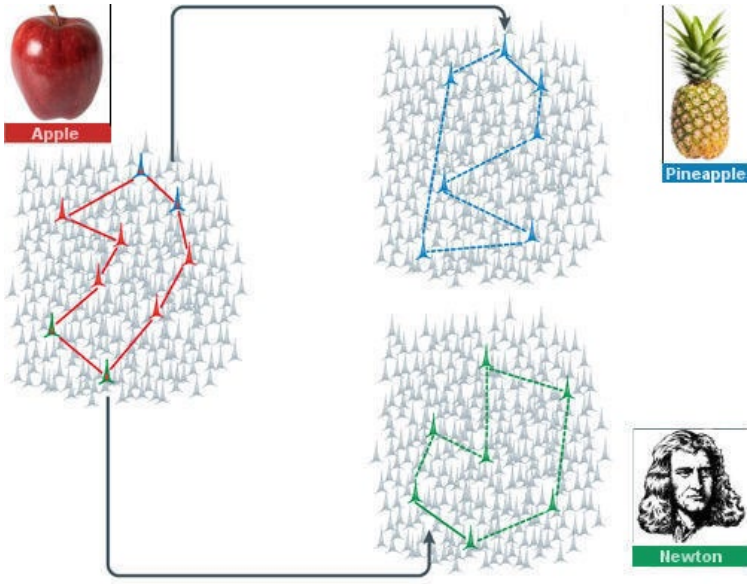
Block 1
Nervcellsfysiologi
Eric Hanse

Action potentials ”in action”

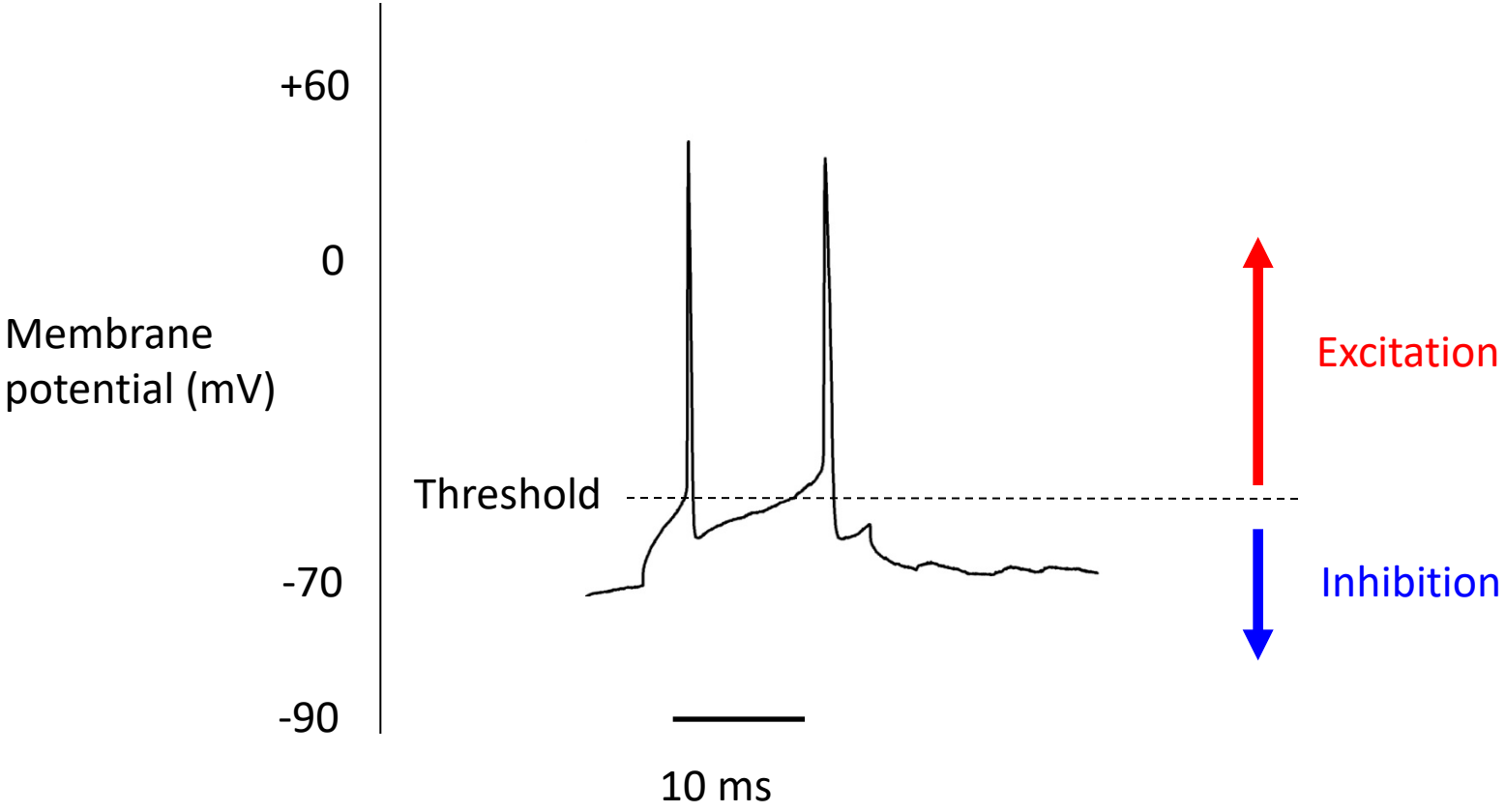
The withdrawal reflex



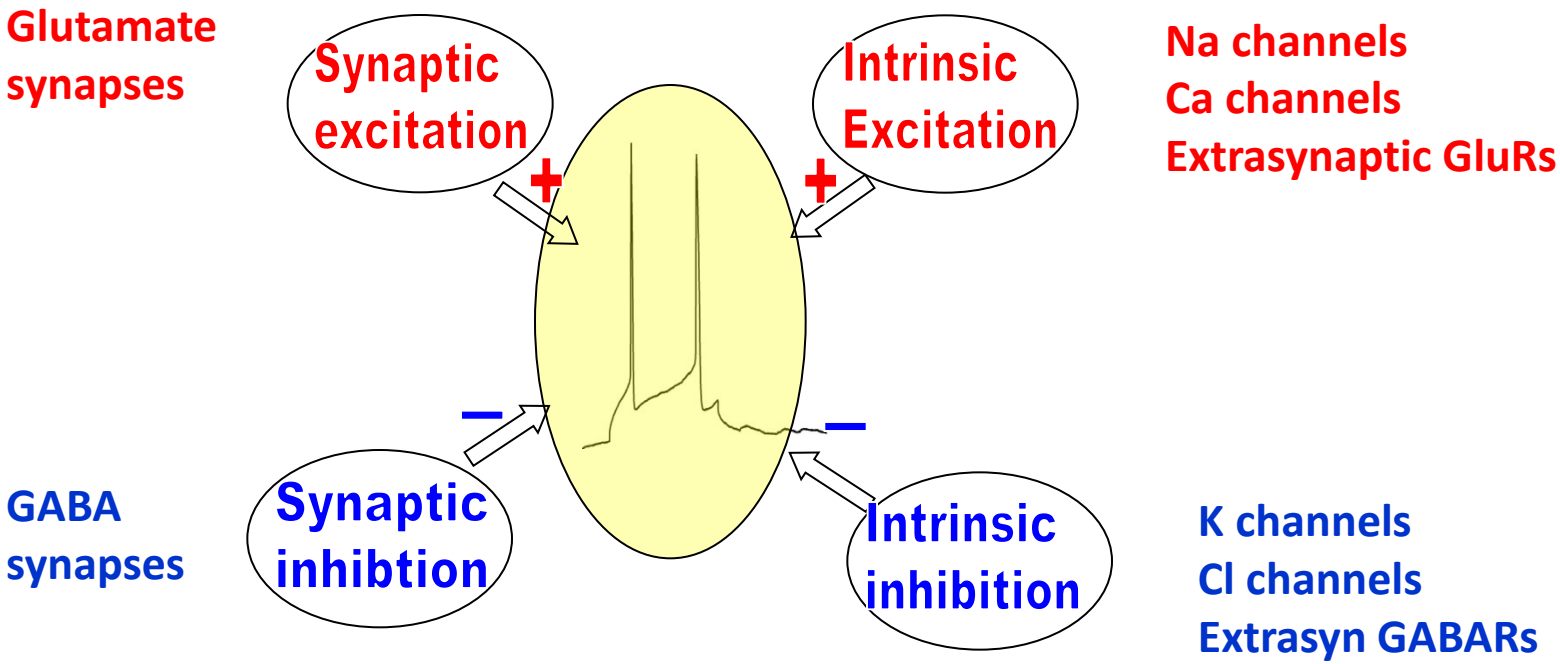
Functional cell assemblies, or engrams



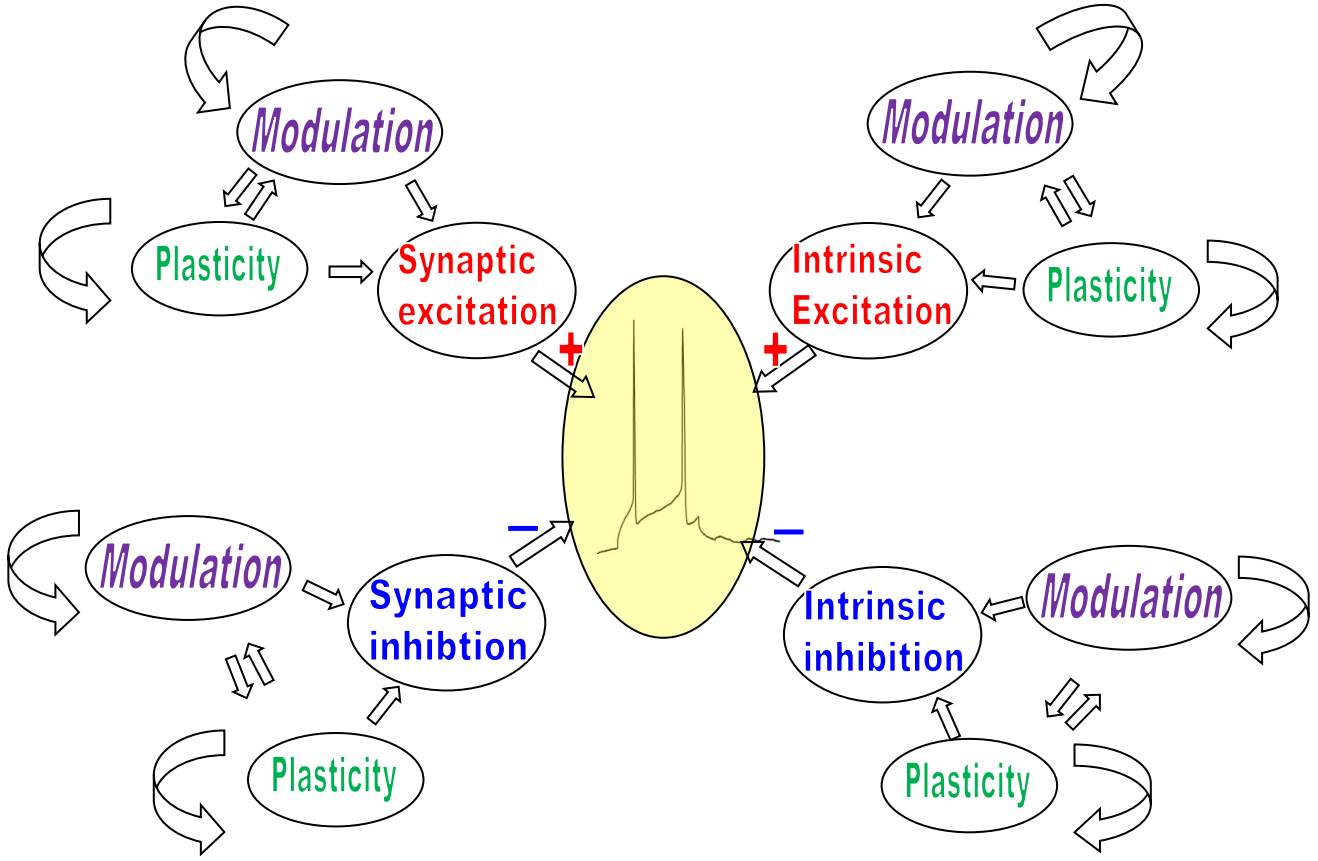
Excitability
– the likelihood of evoking action potentials



Synaptic and Intrinsic Excitability



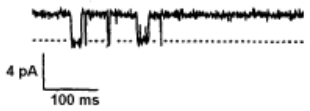
Modulation and Plasticity of Excitability



Plasticity – based on neuronal activity - aims to create / erase engrams
Modulation – based on realease of modulatory neurotransmitters – modulate the accessability of engrams

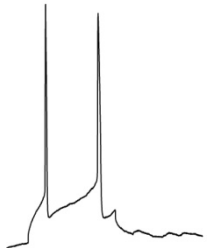
Electrophysiology – different levels of reductionism

Single protein

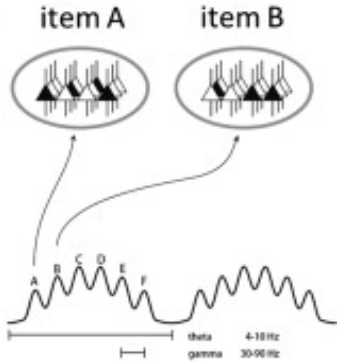


Single synapse

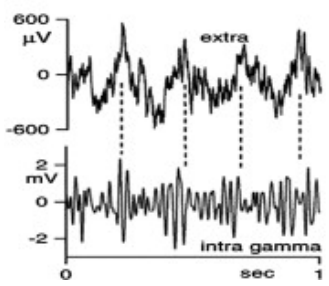
Single cell



Cell assemblies



Network oscillations



Isolated cells

Cell cultures

Brain slices

Brain organoids

In vivo

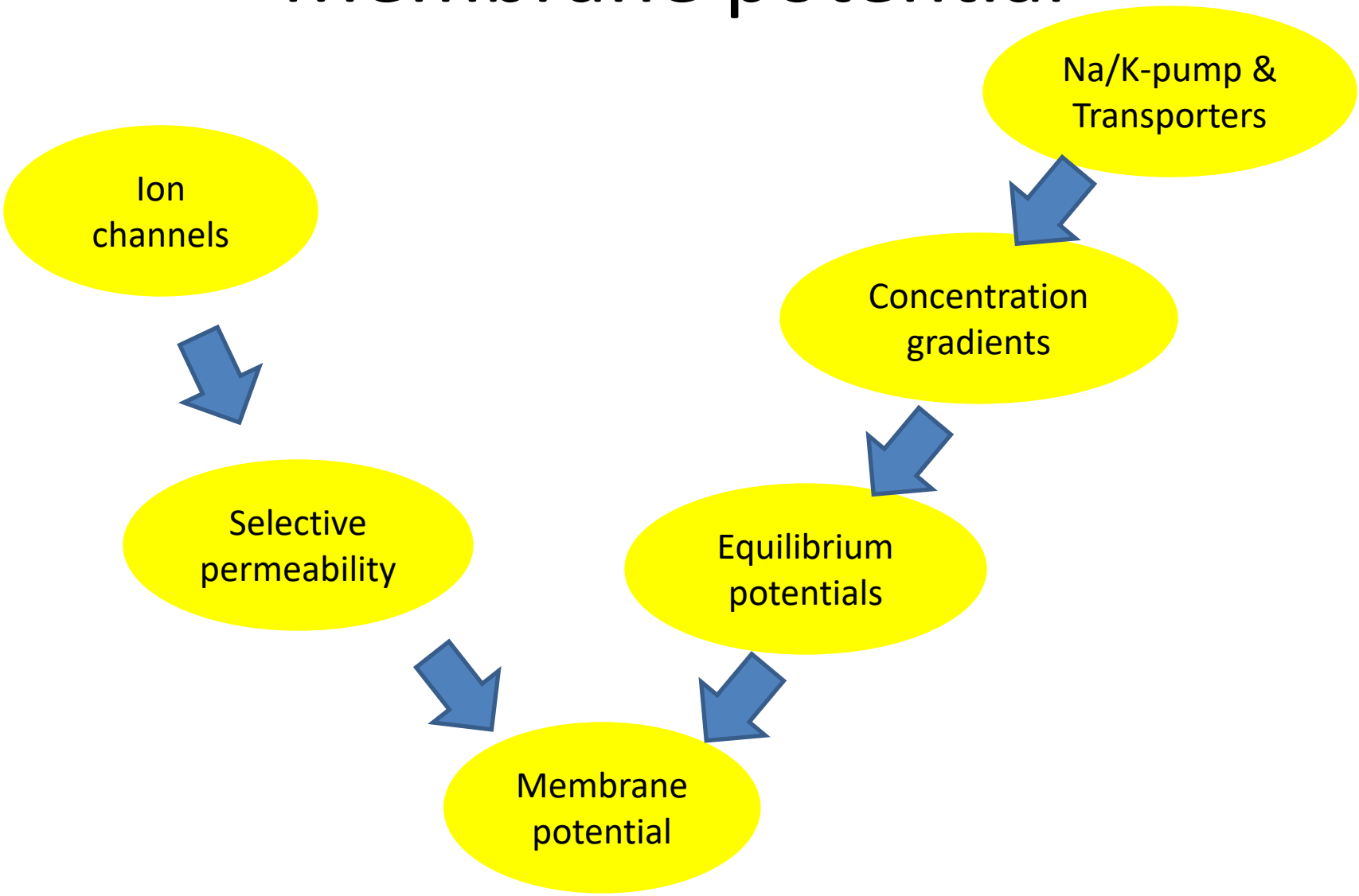
Patch-clamp recordings

Extracellular recordings

Optical recordings

Multielectrode array recordings

Membrane potential



Pumps, concentration differences and equilibrium potential

Nernst equation

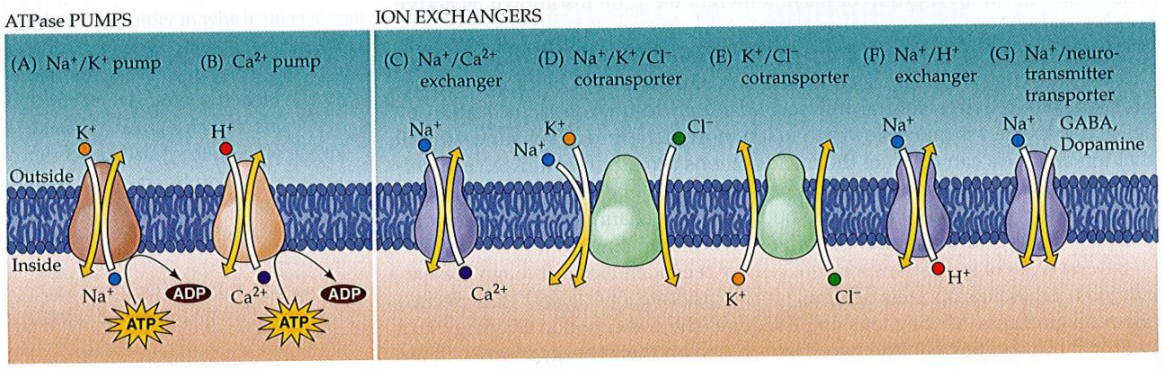
$$E_{jon} = 2.303\ (RT/zF)\ \log({}^{[jon]_u}/_{[jon]_i})$$

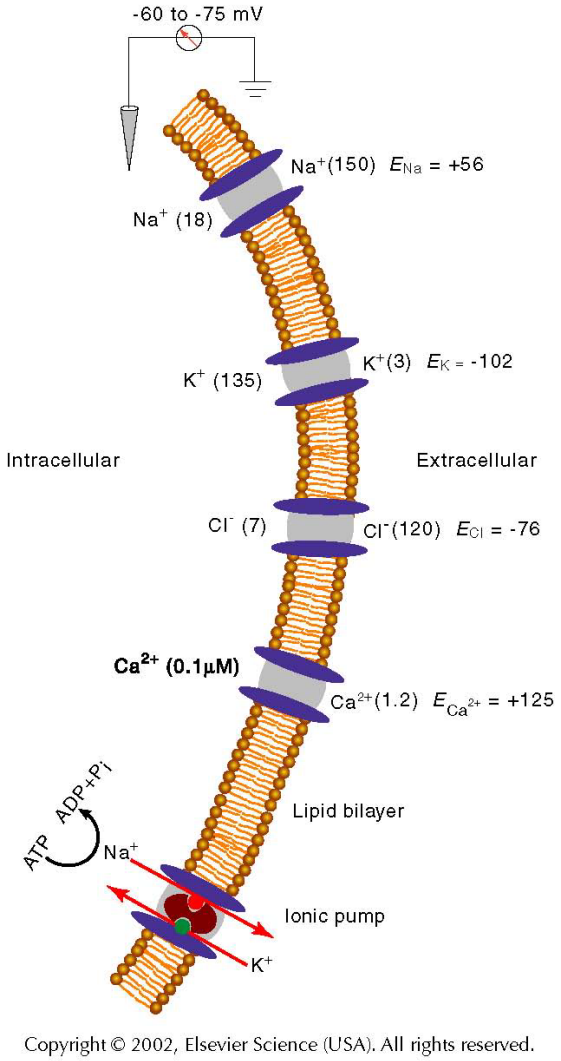
$$E_{jon} = 61.54\ \log({}^{[jon]_u}/_{[jon]_i})$$

Ion concentrations in human cerebrospinal fluid and serum (in mM)

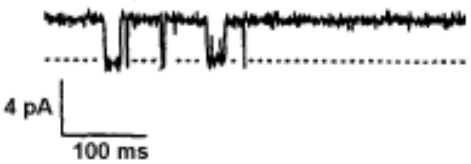
	Cerebrospinal fluid	Serum	Correlation
K^+	2.9	4.2	No
Na^+	147	140	Yes
Cl^-	125	100	No
Ca^{2+} Total	1.2	2.4	Yes
Ca^{2+} Free	1.0	1.2	
Mg^{2+} Total	1.2	0.8	No
Mg^{2+} Free	1.0	0.5	

Lyckenvik et al (2025) Brain Commun 24:fcaf201

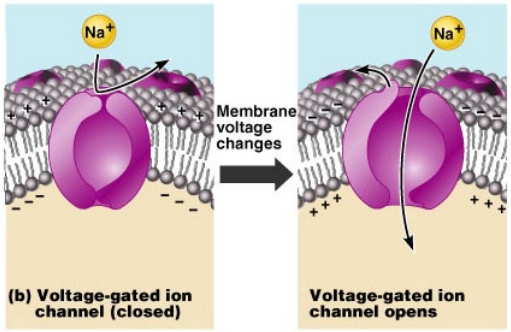


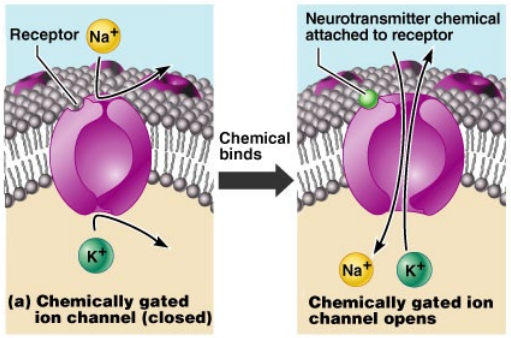


Ion channels

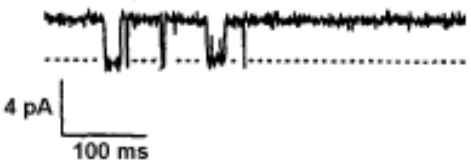


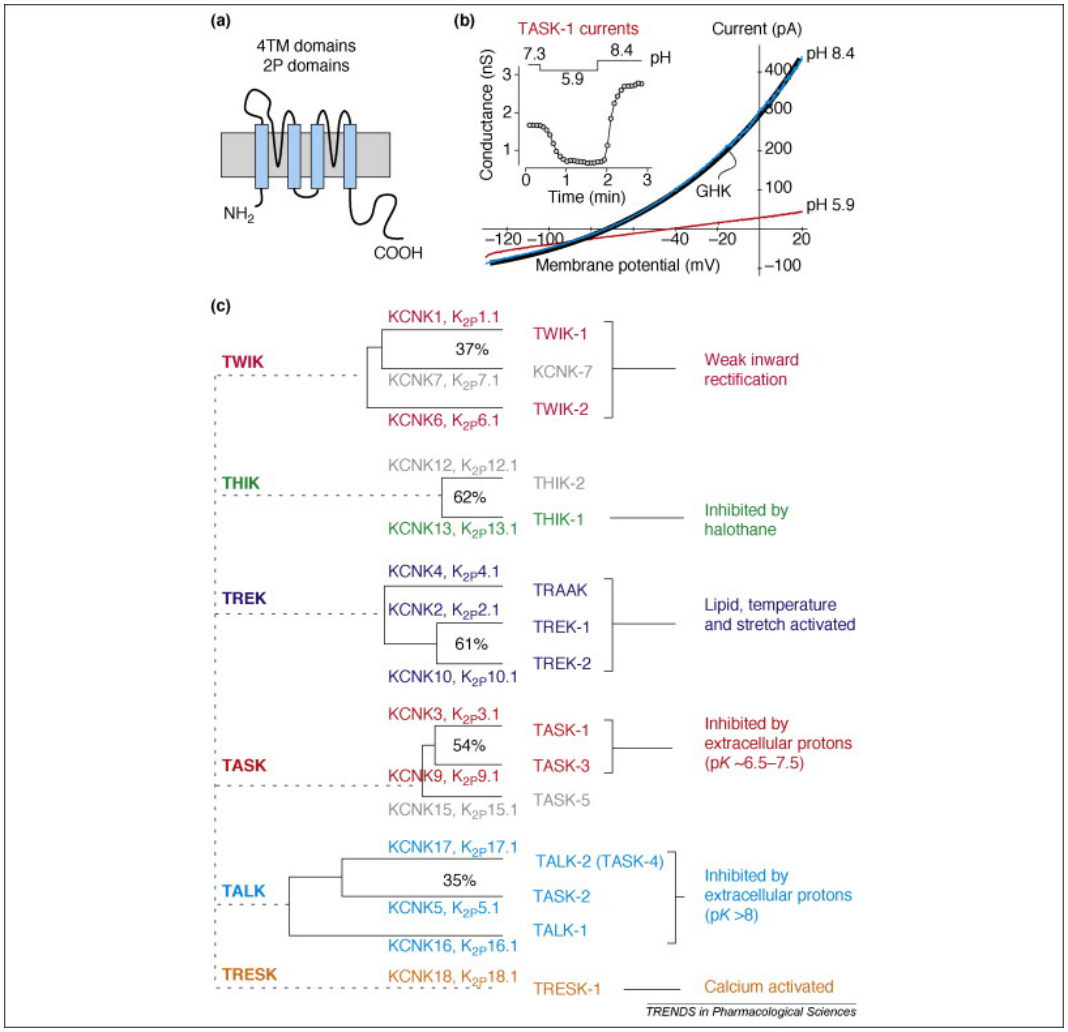
		Gating						
		Voltage	Ligand	Ca^{2+}, cAMP, cGMP	Temp	Mech	H^+	"leak"
Selectivity	Na							
	K							
	N/K							
	N/K/Ca							
	Ca^{2+}							
	Cl/HCO_3							





Leak channels





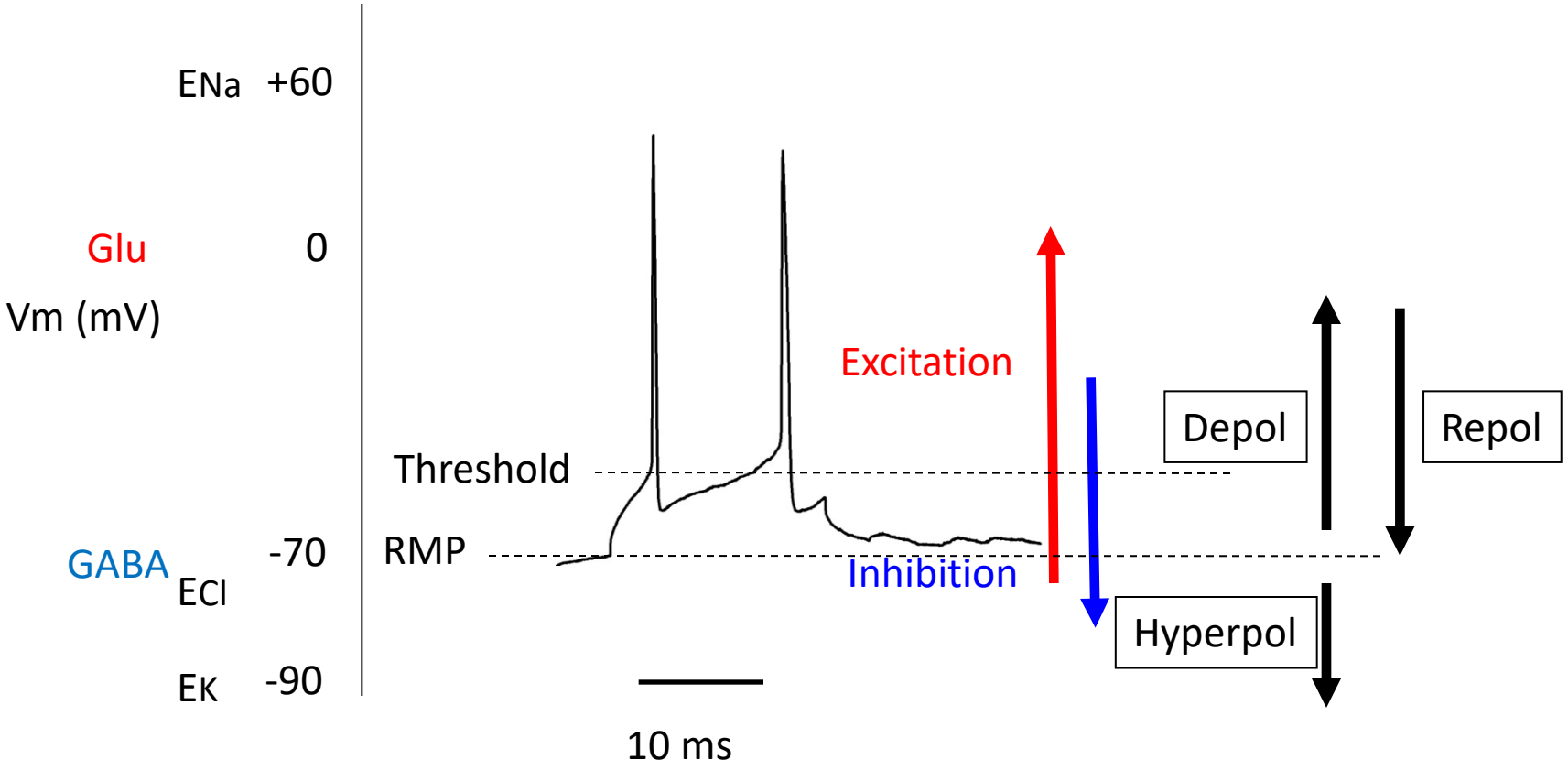
The resting permeability for K^+ is much higher than for Na^+, but the driving force (at resting membrane potential) is much higher for Na^+ than for K^+. The resultant currents for K^+ and Na^+ are therefore equal

The Sodium "Leak" Has Finally Been Plugged

Neuron *54*, May 24, 2007

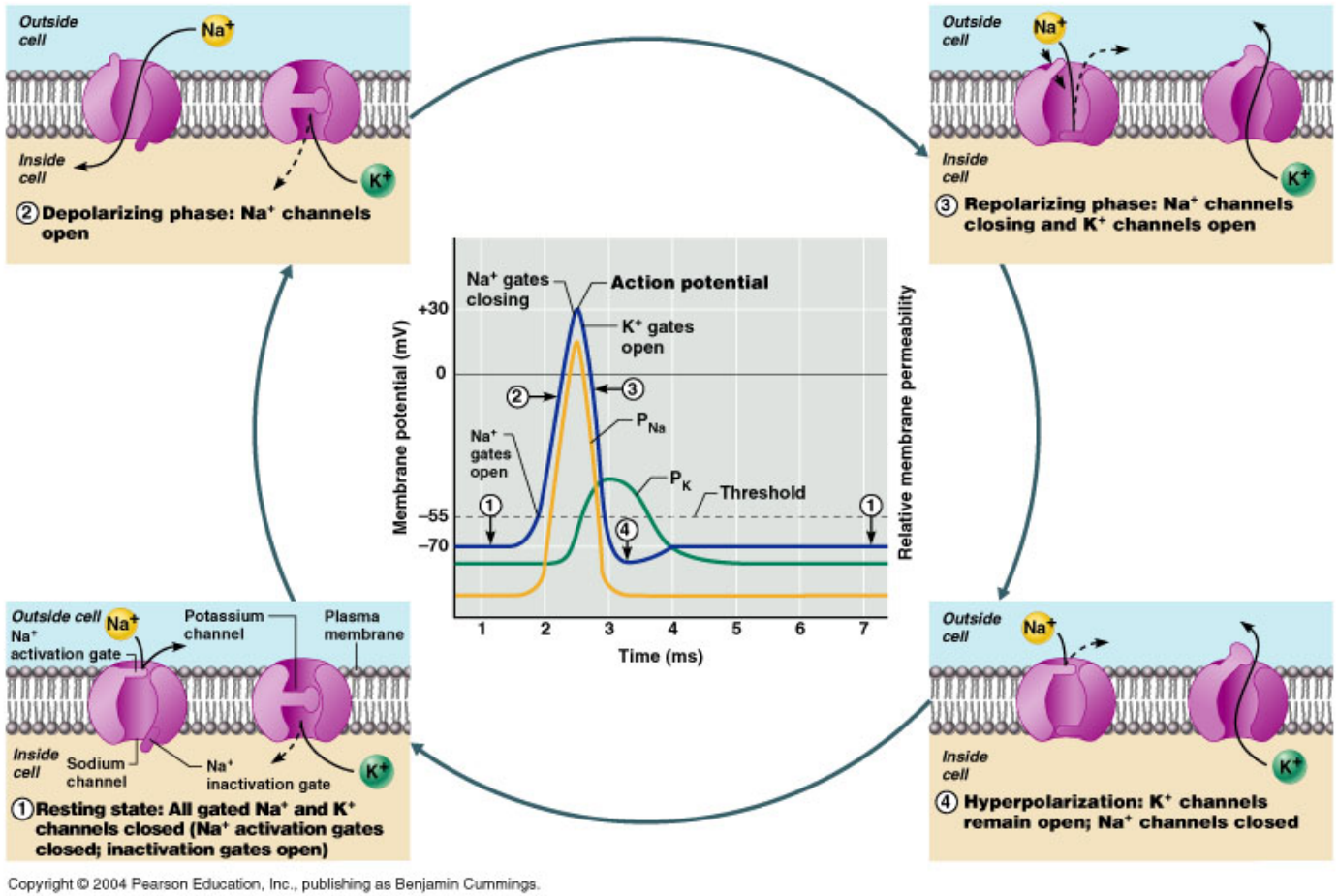
Trends in Pharmacological Sciences (2008) 29:11

Membrane potential



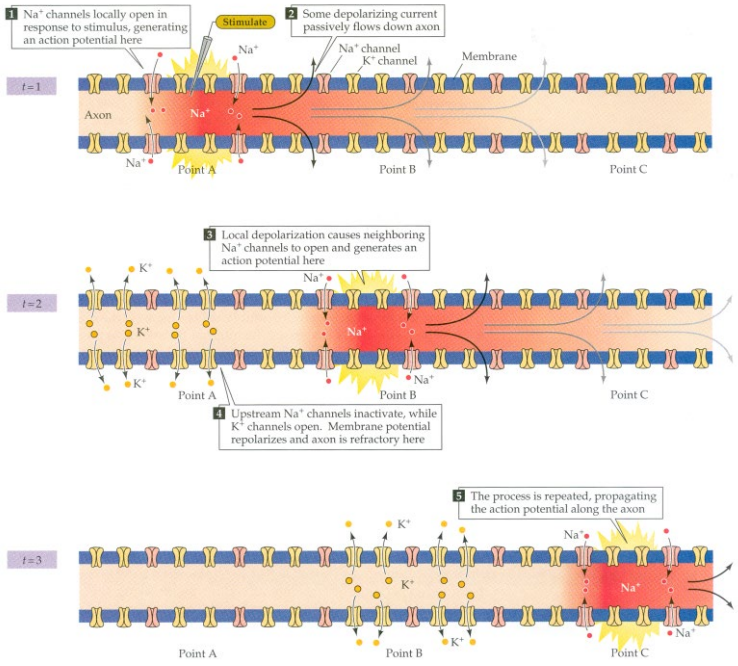
The Goldman equation $V_m = 61.54 \text{ mV} \log \frac{P_K [K^+]_u + P_{Na}[Na^+]_u}{P_K [K^+]_i + P_{Na}[Na^+]_i}$

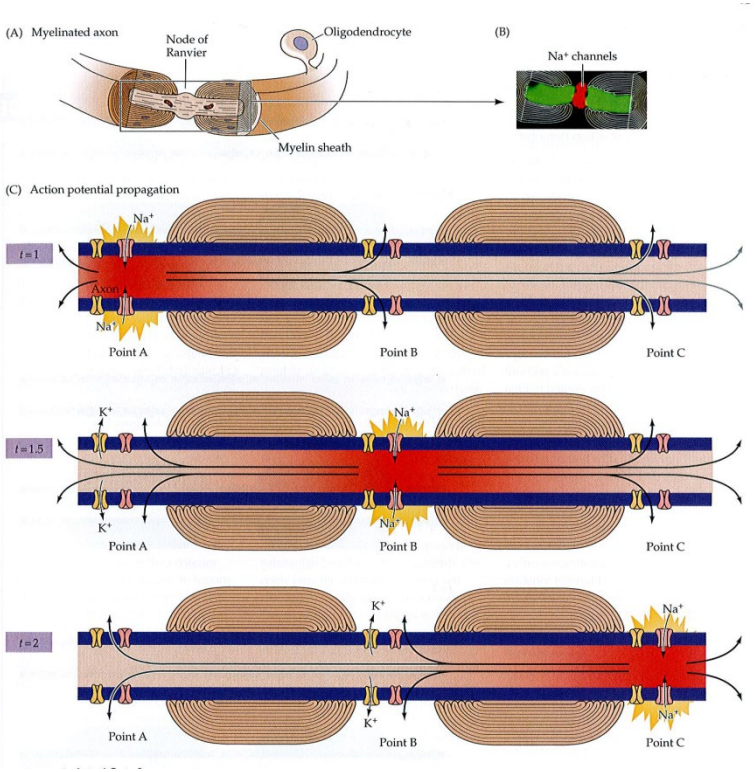
Action potential – ”all-or-none”



Voltage-gated sodium channels are blocked by local anaesthetics and tetrodotoxin

Propagation of the action potential

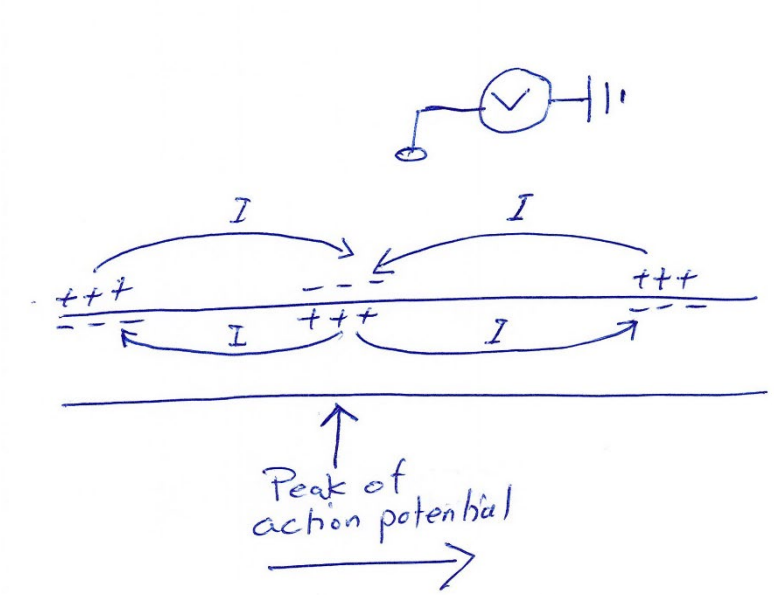




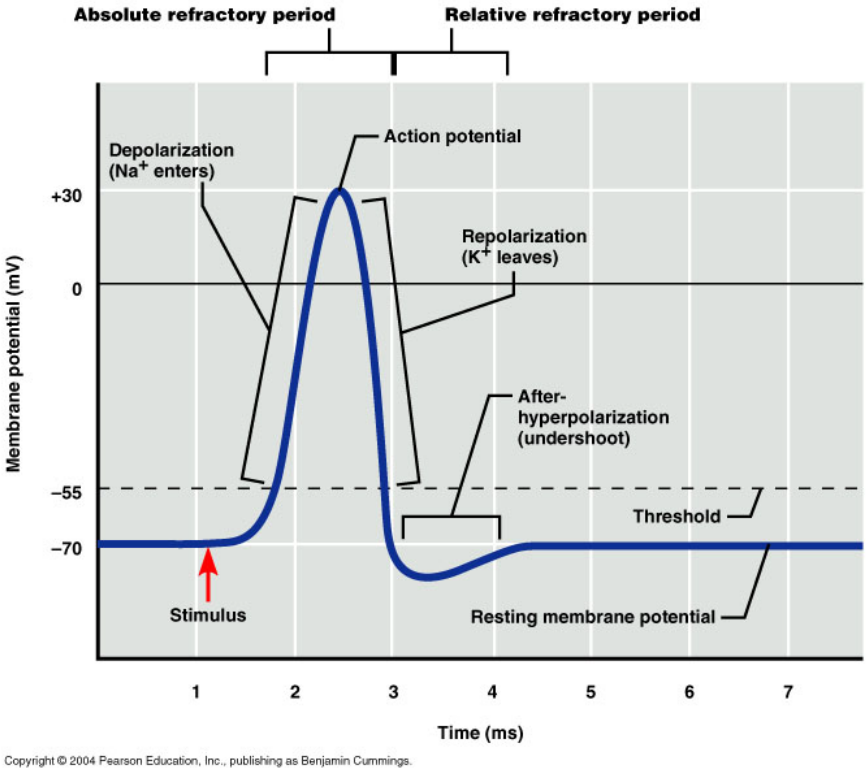
Myelin
Diameter
Temperatur

	Muscle nerve	Cutaneous nerve	Fiber diameter (μm)	Conduction velocity (ms)
Myelinated				
Large	I	A–C	13–20	80–120
Small	II	Aβ	6–12	35–75
Smallest	III	Aδ	1–5	5–30
Unmyelinated	IV	C	0.2–1.5	0.5–2

Extracellular recording of action potentials



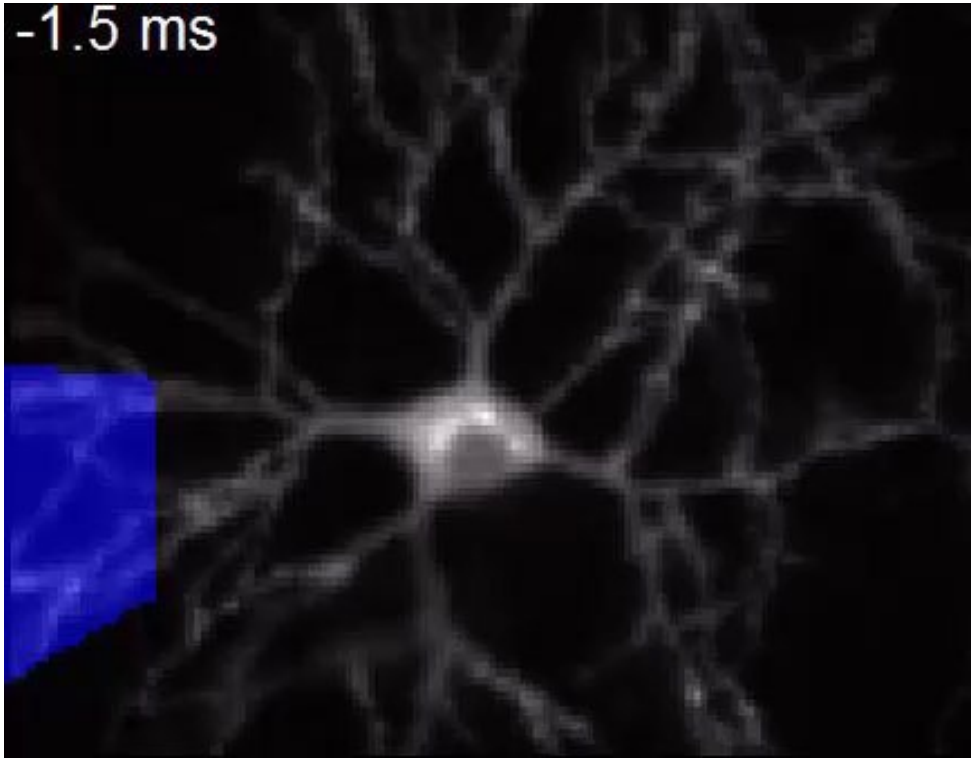
Refractory period following the action potential



Absolute refractory period = Voltage-gated Na^+-channels are inactivated, making a new action potential impossible.

Relative refractory period = Voltage-gated Na^+-channels de-inactivates during this period and the membrane potential is hyperpolarized. A stronger than normal depol is required to evoke an action potential.

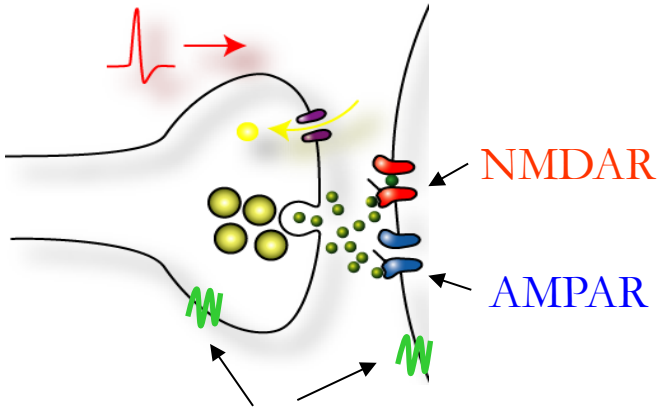
Optical recording of the action potential

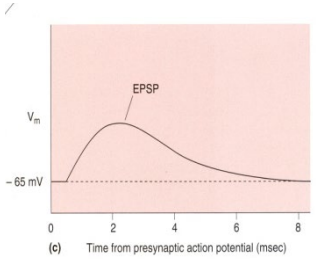


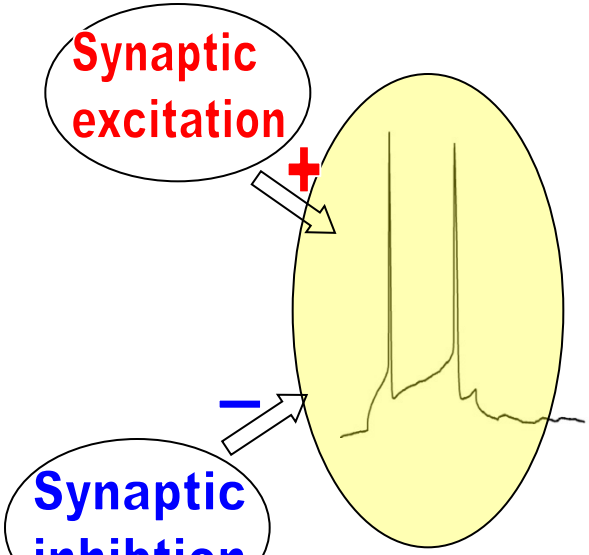
Hochbaum et al (2014) **All-optical electrophysiology in mammalian neurons using engineered microbial rhodopsins** *Nature Methods* 11: 825-833

Synaptic excitation and inhibition

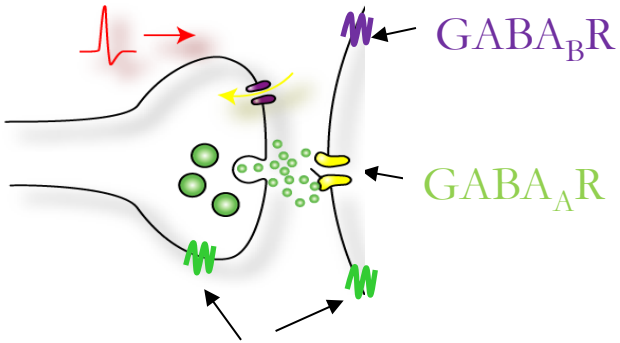
Excitatory synapse

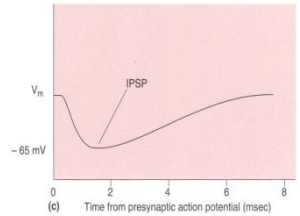




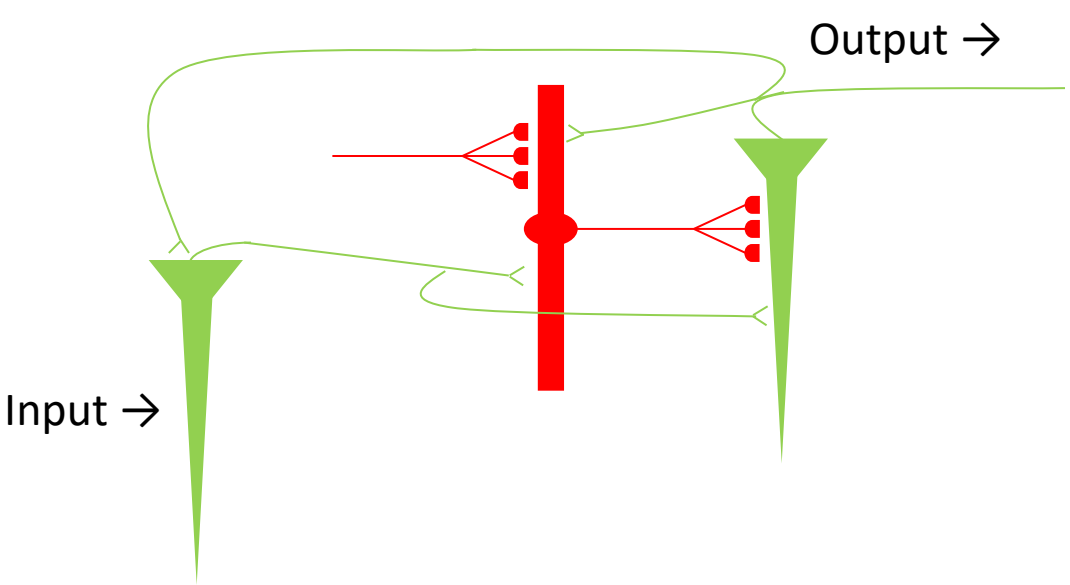


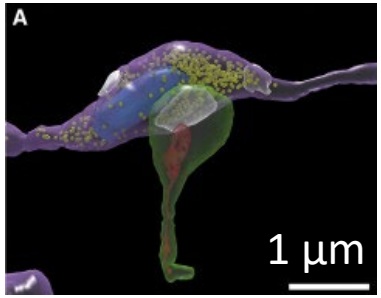
Inhibitory synapse



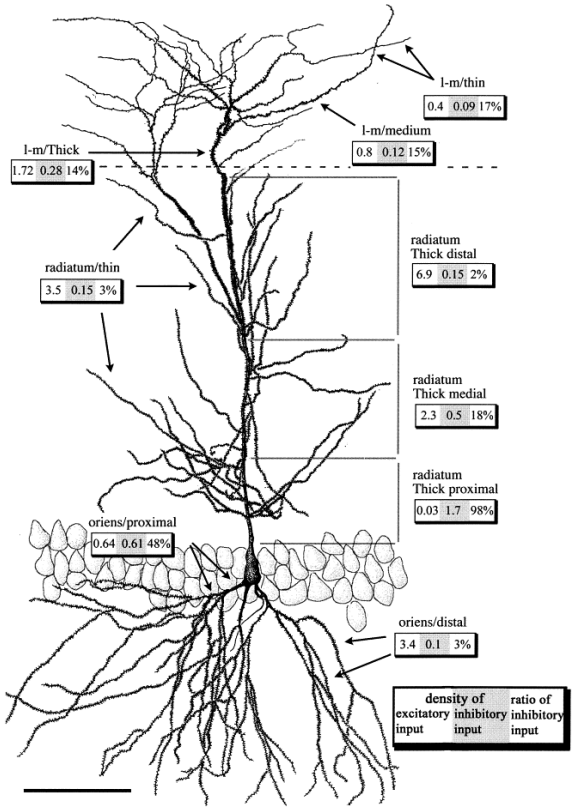


Glu and GABA synapses





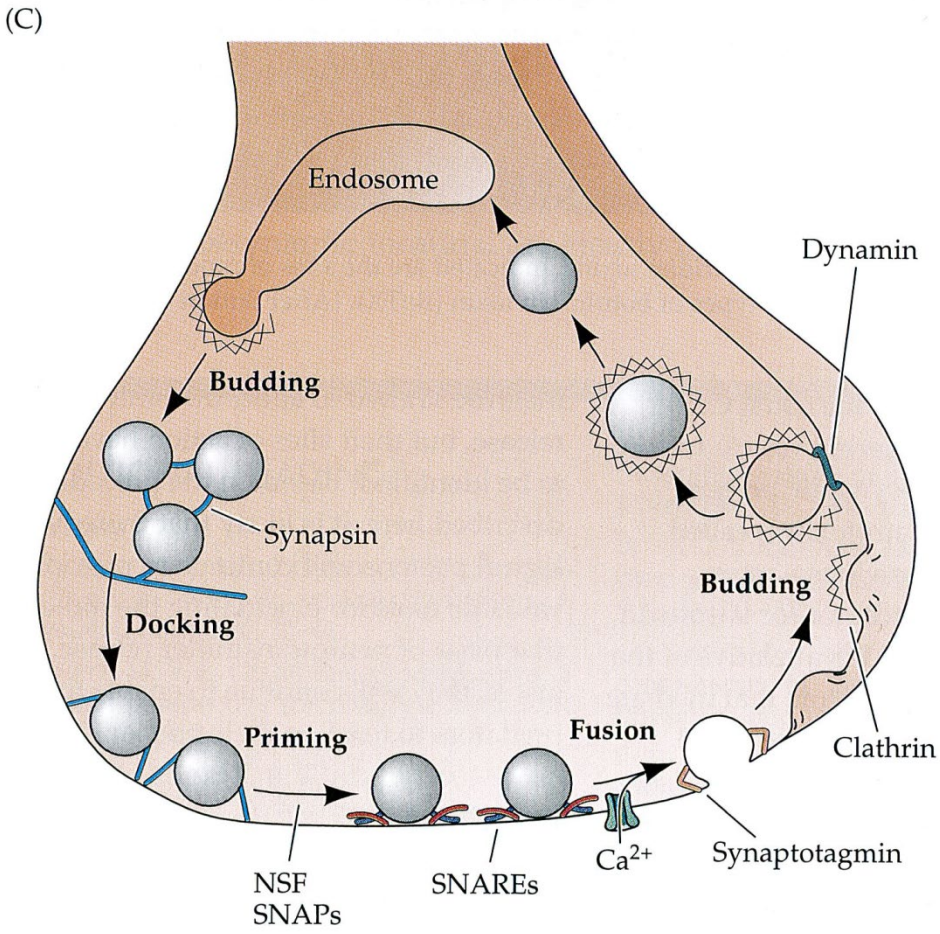
Kasthuri et al (2015) **Saturated reconstruction of a volume of neocortex** Cell 162: 648661



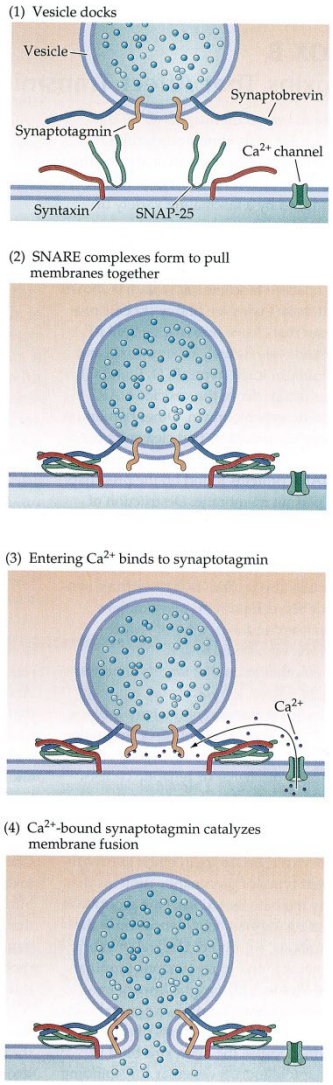
Cortical pyramidal cell:
ca. 30000 Glutamate synapses (90%)
ca. 2000 GABA synapses (10%)

Megías, Emri, Freund & Gulyás (2001) Neuroscience 102:527

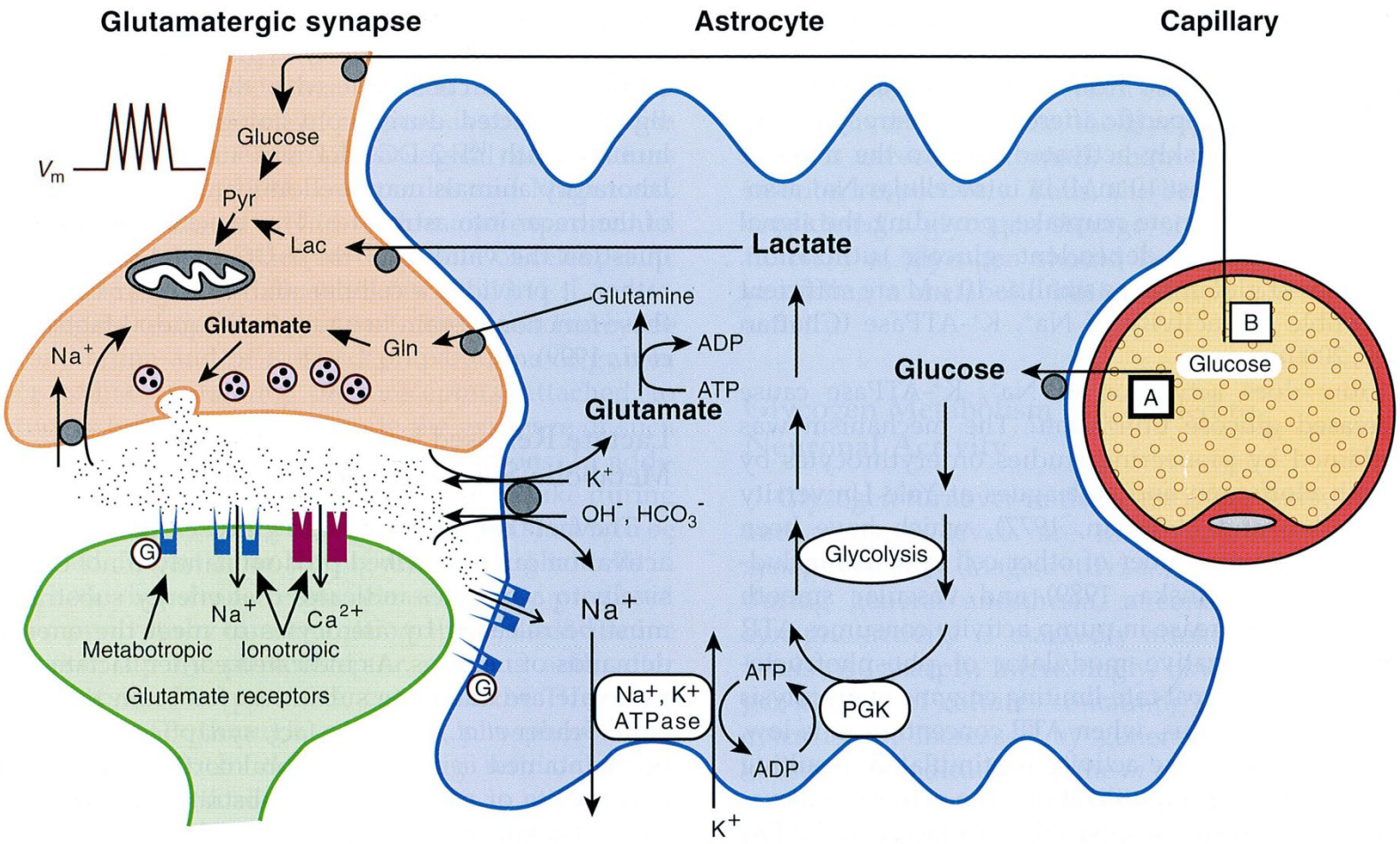
Presynaptic release of transmitter vesicle



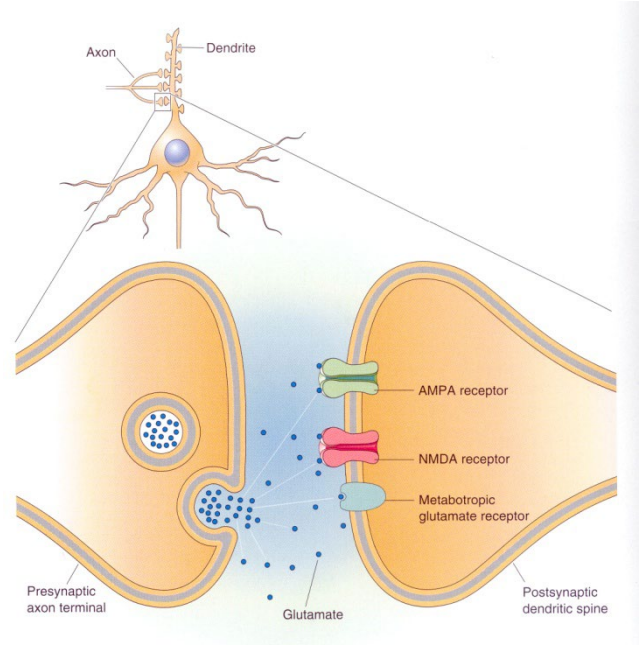
SNARE-mediated exocytosis

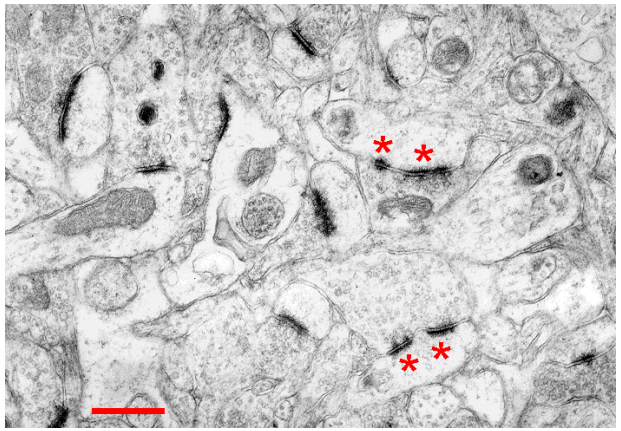


Glutamate uptake in astrocytes



Synapses are usually small and unreliable, but many (and plastic)





1 µm

3 quantal parameters determine the signalling strength of a synaptic connection

Synaptic strength = *n* x *p* x *q*

***n* = no. of release sites**

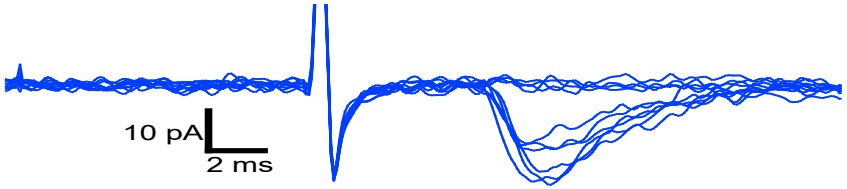
***p* = release probability**

The probability that an action potential will cause the release of one vesicle

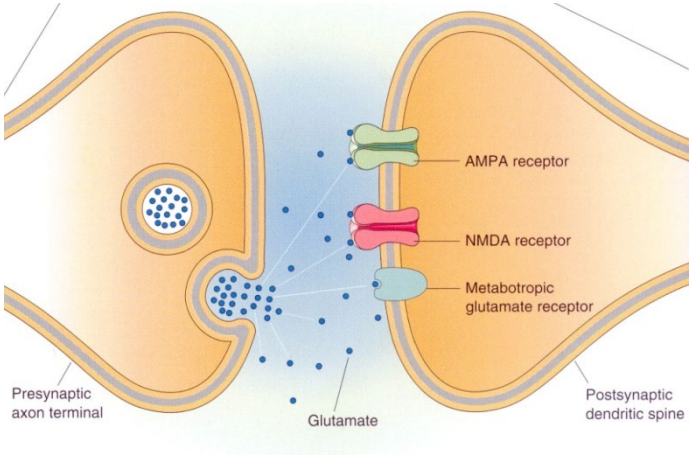
***q* = quantal size**

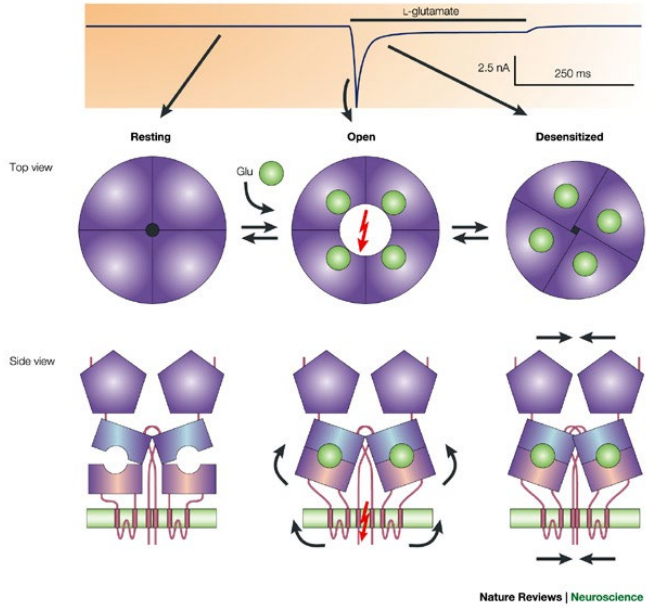
The magnitude of the postsynaptic response to one vesicle

Recording from one synapse



The Glutamate synapse

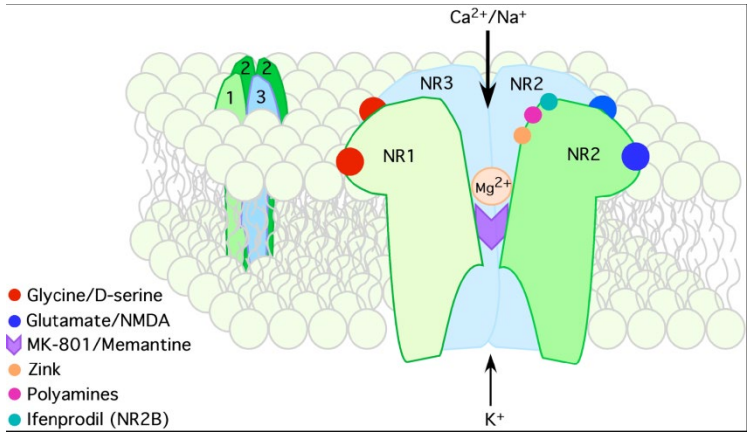




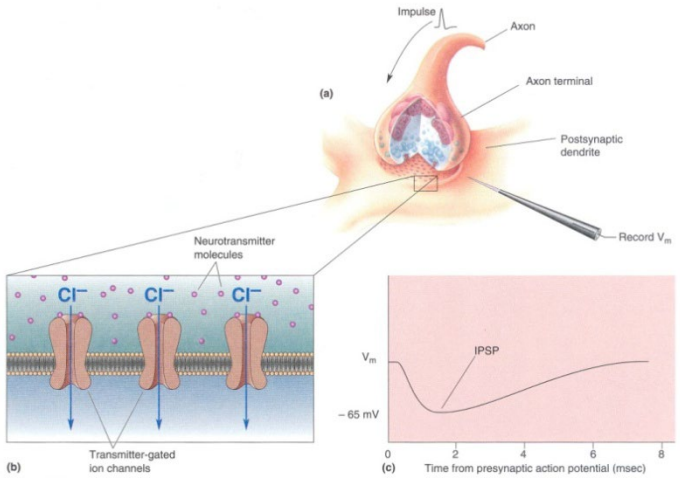
1. The AMPA receptor channel:
-opened by glutamate
-permeates Na^+ and K^+
-gives rise to a brief (ca. 10 ms) EPSP

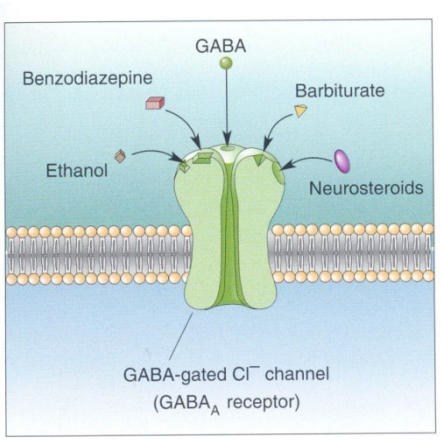
2. The NMDA receptor channel:
-opened by glutamate (and Gly/D-Ser) + depol
-permeates Na^+, K^+ and Ca^{2+}
- gives rise to a brief long-lasting (ca. 100 ms) EPSP
-is necessary for the induction of synaptic plasticity; Long-term potentiation (LTP) och long-term depression (LTD).

3. Metabotropic glutamate receptors (mGluRs) are G-protein coupled receptors that, for example, can give rise to Ca^{2+} release from ER and facilitate synaptic plasticity.



The GABA synapse





$GABA_A$ Rec

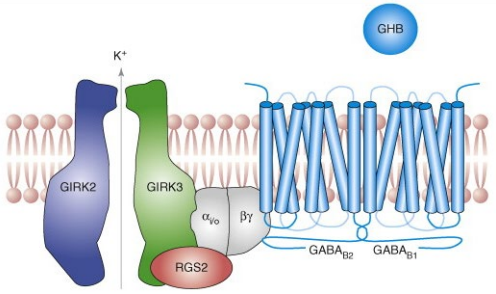
Article

Resolving native $GABA_A$ receptor structures from the human brain

https://doi.org/10.1038/s41586-024-08454-1
Received: 30 June 2024
Accepted: 26 November 2024
Published online: 22 January 2025
Check for updates

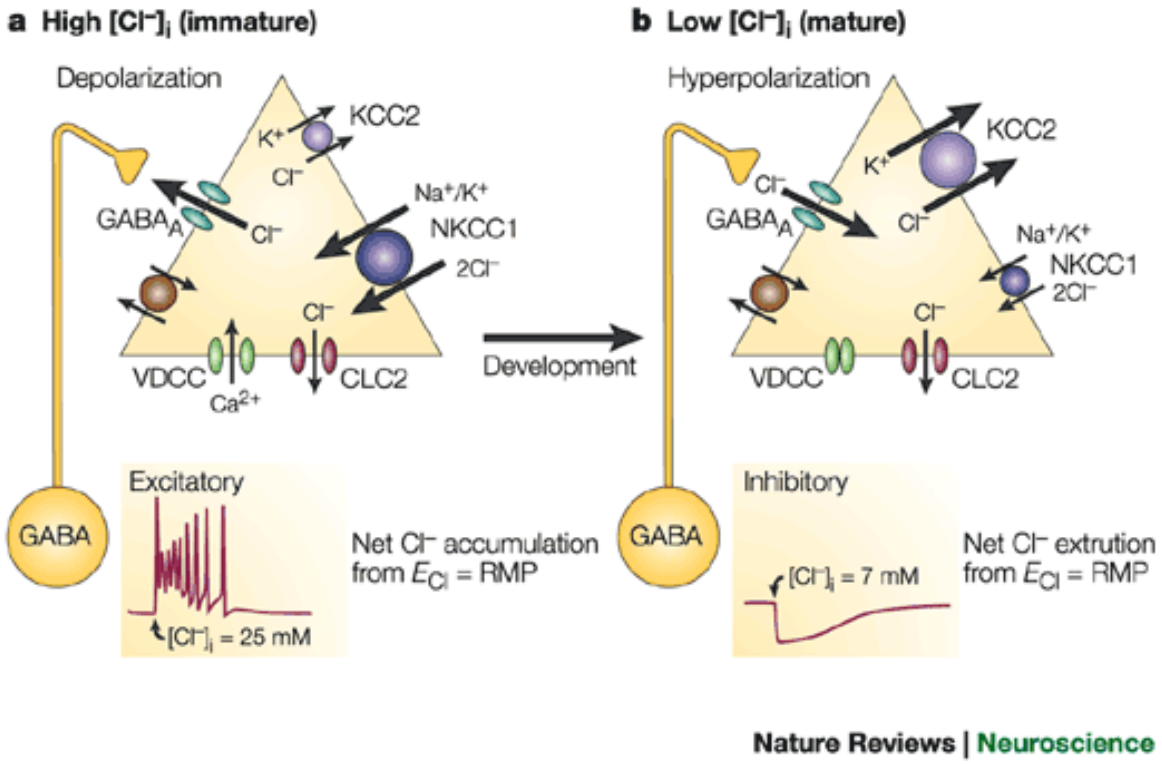
Jia Zhou[1], Colleen M. Noviello[1], Jinfeng Teng[1], Haley Moore[2], Bradley Lega[3] & Ryan E. Hibbs[1,4]

Type A GABA (γ-aminobutyric acid) receptors ($GABA_A$ receptors) mediate most fast inhibitory signalling in the brain and are targets for drugs that treat epilepsy, anxiety, depression and insomnia and for anaesthetics[1,2]. These receptors comprise a complex array of 19 related subunits, which form pentameric ligand-gated ion channels. The composition and structure of native $GABA_A$ receptors in the human brain have been inferred from subunit localization in tissue[1,3], functional measurements and structural analysis from recombinant expression[4–7] and in mice[8]. However, the arrangements of subunits that co-assemble physiologically in native human $GABA_A$ receptors remain unknown. Here we isolated α1 subunit-containing $GABA_A$ receptors from human patients with epilepsy. Using cryo-electron microscopy, we defined a set of 12 native subunit assemblies and their 3D structures. We address inconsistencies between previous native and recombinant approaches, and reveal details of previously undefined subunit interfaces. Drug-like densities in a subset of these interfaces led us to uncover unexpected activity on the $GABA_A$ receptor of antiepileptic drugs and resulted in localization of one of these drugs to the benzodiazepine-binding site. Proteomics and further structural analysis suggest interactions with the auxiliary subunits neuroligin 2 and GARLH4, which localize and modulate $GABA_A$ receptors at inhibitory synapses. This work provides a structural foundation for understanding $GABA_A$ receptor signalling and targeted pharmacology in the human brain.

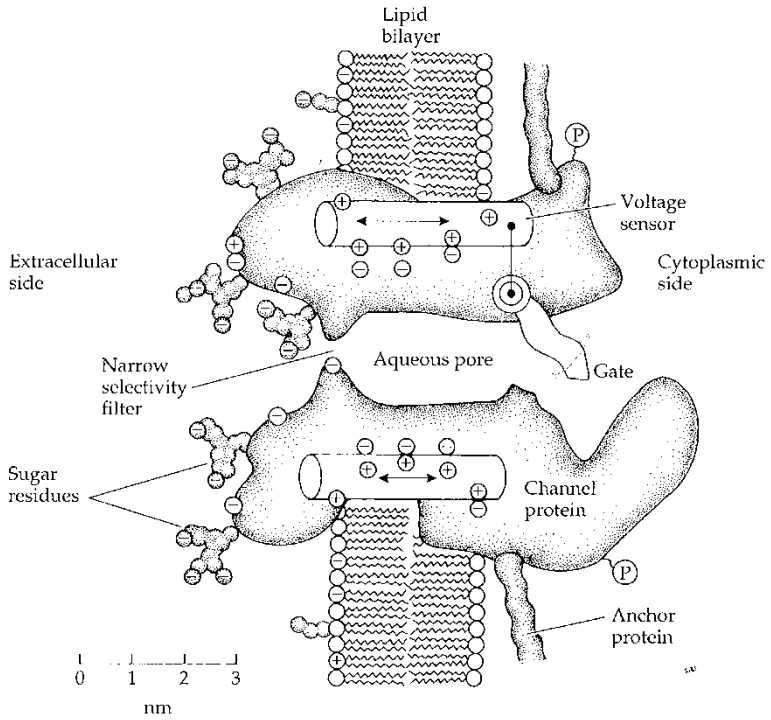


$GABA_B$ Rec

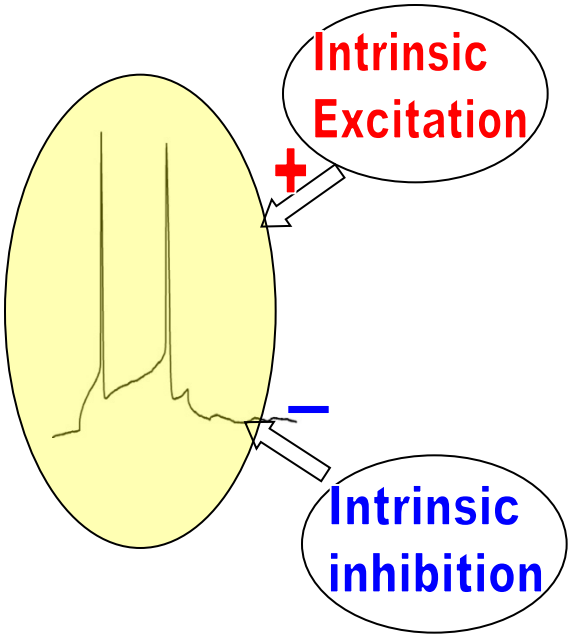
The i.c. Cl^- concentration determines the response of the $GABA_A$ receptor channels



Intrinsic excitability – all ion channels of the neuron, except the ligand-gated in the synapses

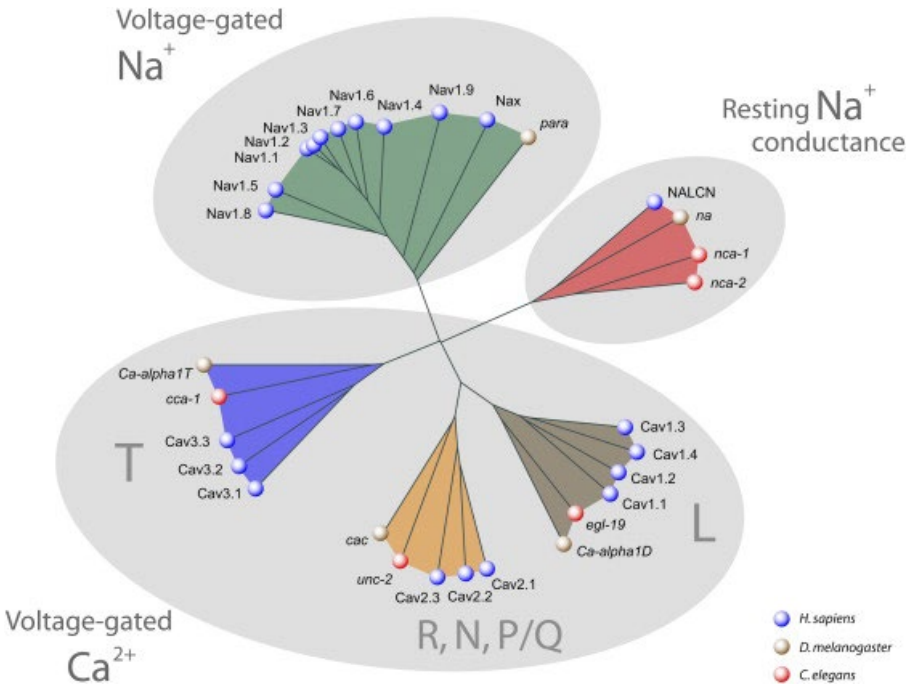


From Hille ”Ion channels in excitable membranes”

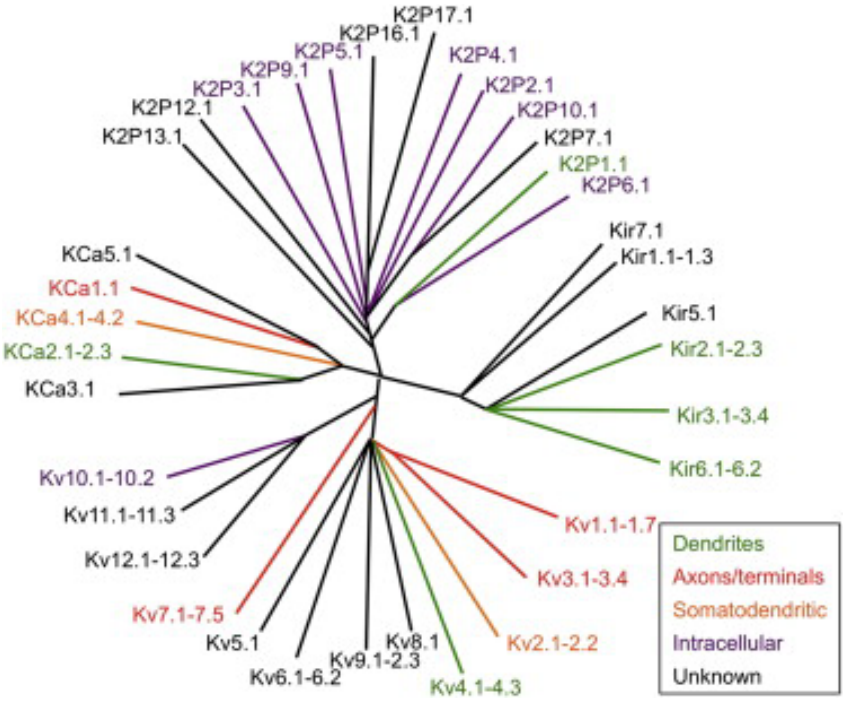


E.c. Calcium blocks
voltage-gated sodium channels

Families of voltage-gated Na^+, Ca^{2+} and K^+ channels



Voltage-gated K-channels



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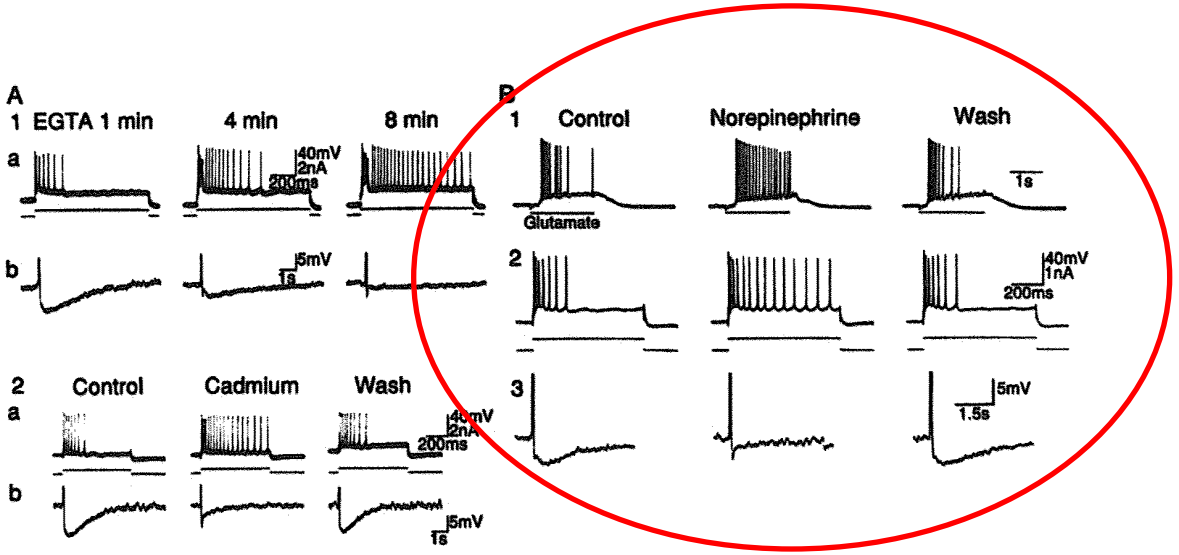
Regulation of action potential frequency – AfterHyperPolarisation (AHP) and gKca^{2+}



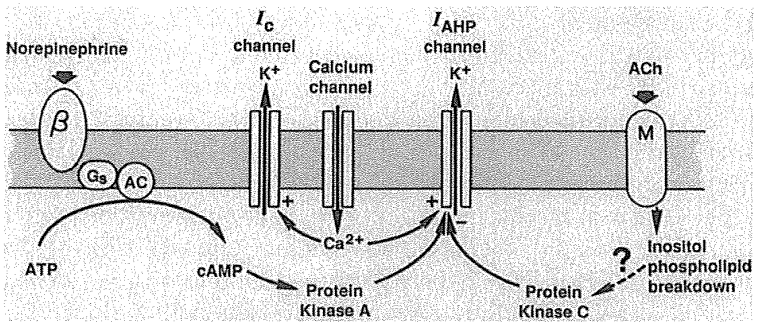


Fig. 2. Diagram of the proposed mechanisms of action of norepinephrine and acetylcholine in blocking the slow Ca^{2+}-activated K^+ conductance.

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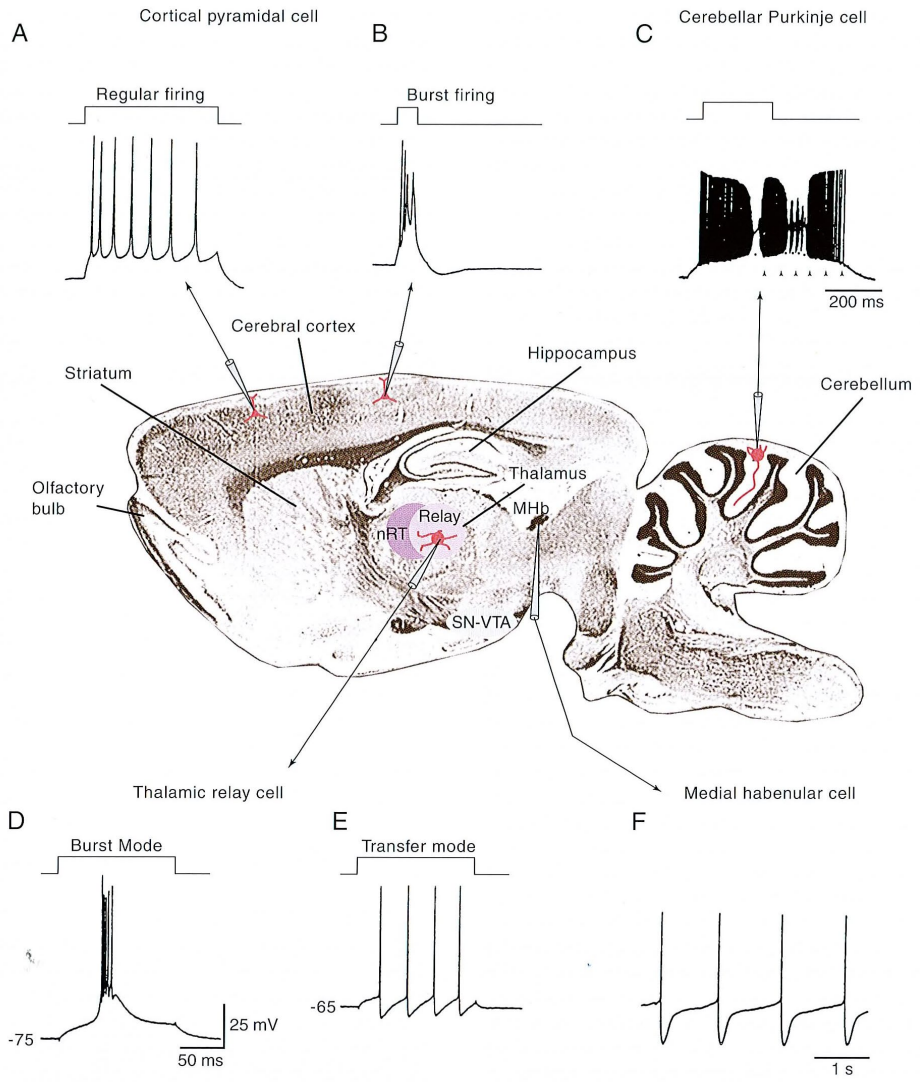
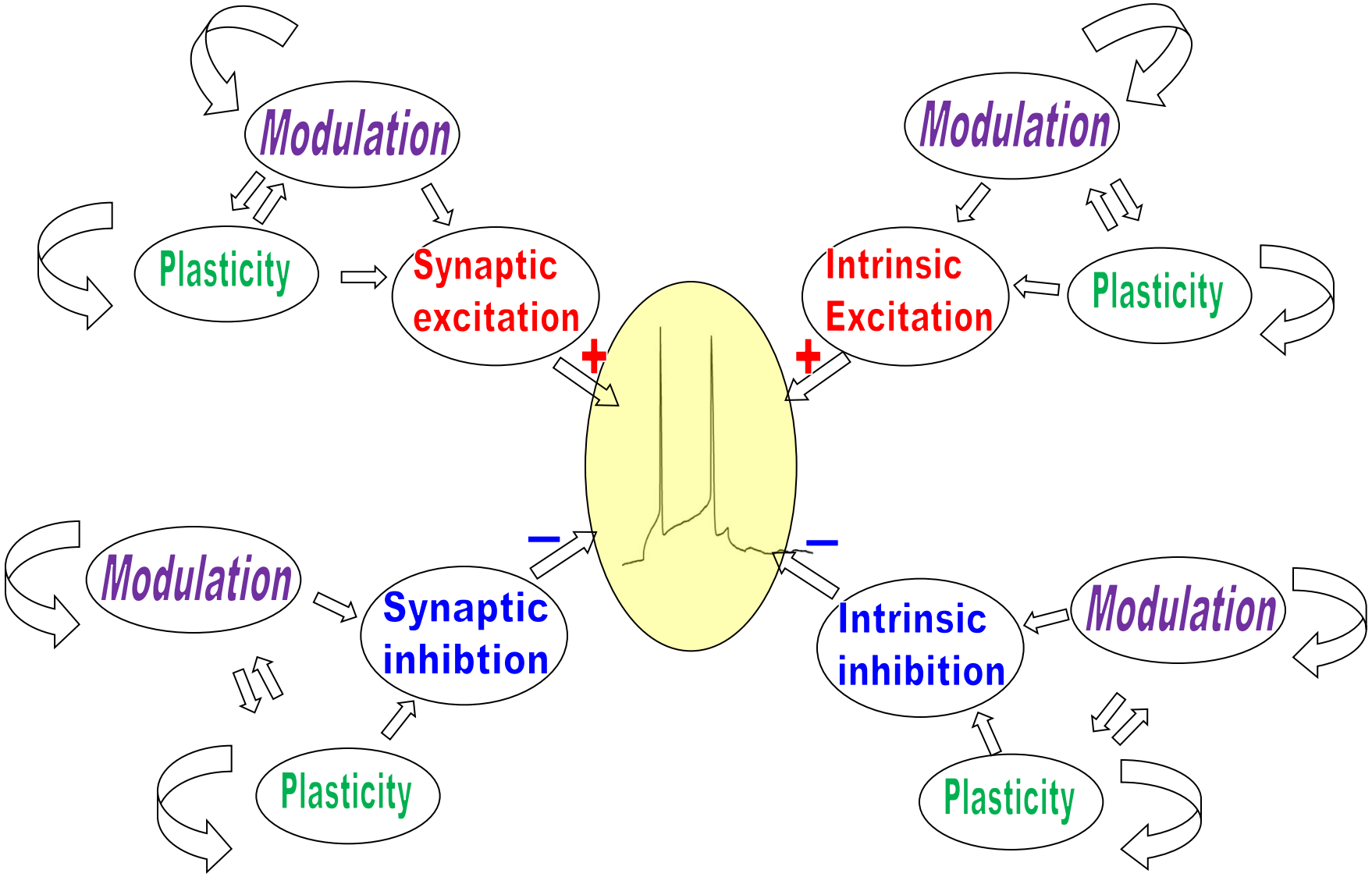
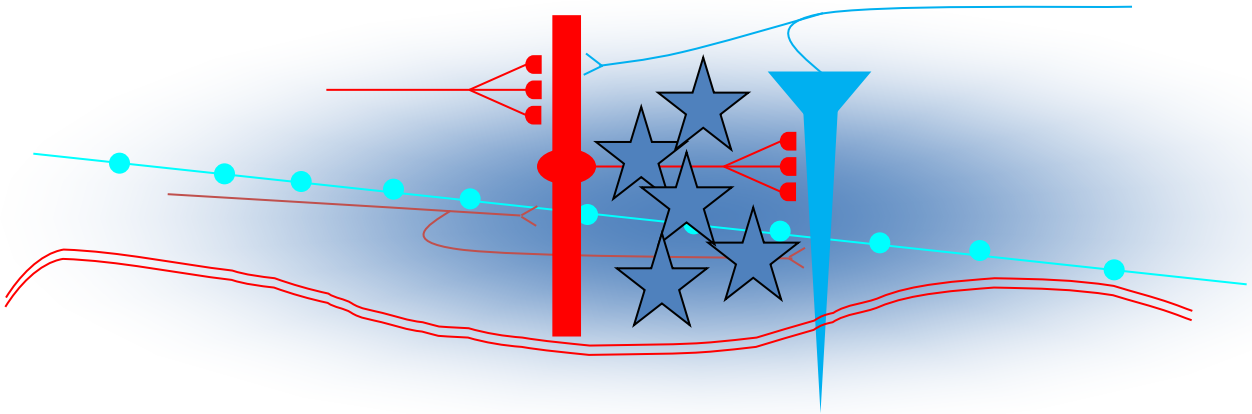
Different firing patterns because of differences in intrinsic excitability



Modulation and Plasticity of Excitability



Neuromodulation



Modulate:
***Release probability**
***Intrinsic excitability**
***Plasticity**

Co-transmitters "Classical"
ACh, NA, 5-HT, Histamin, DA

Co-transmitters Peptides
Orexin, Galanin, Endorphin, CCK, VIP, Oxytocin…

Retrograde transmitters
endocannabinoids, NO, neurotrophins

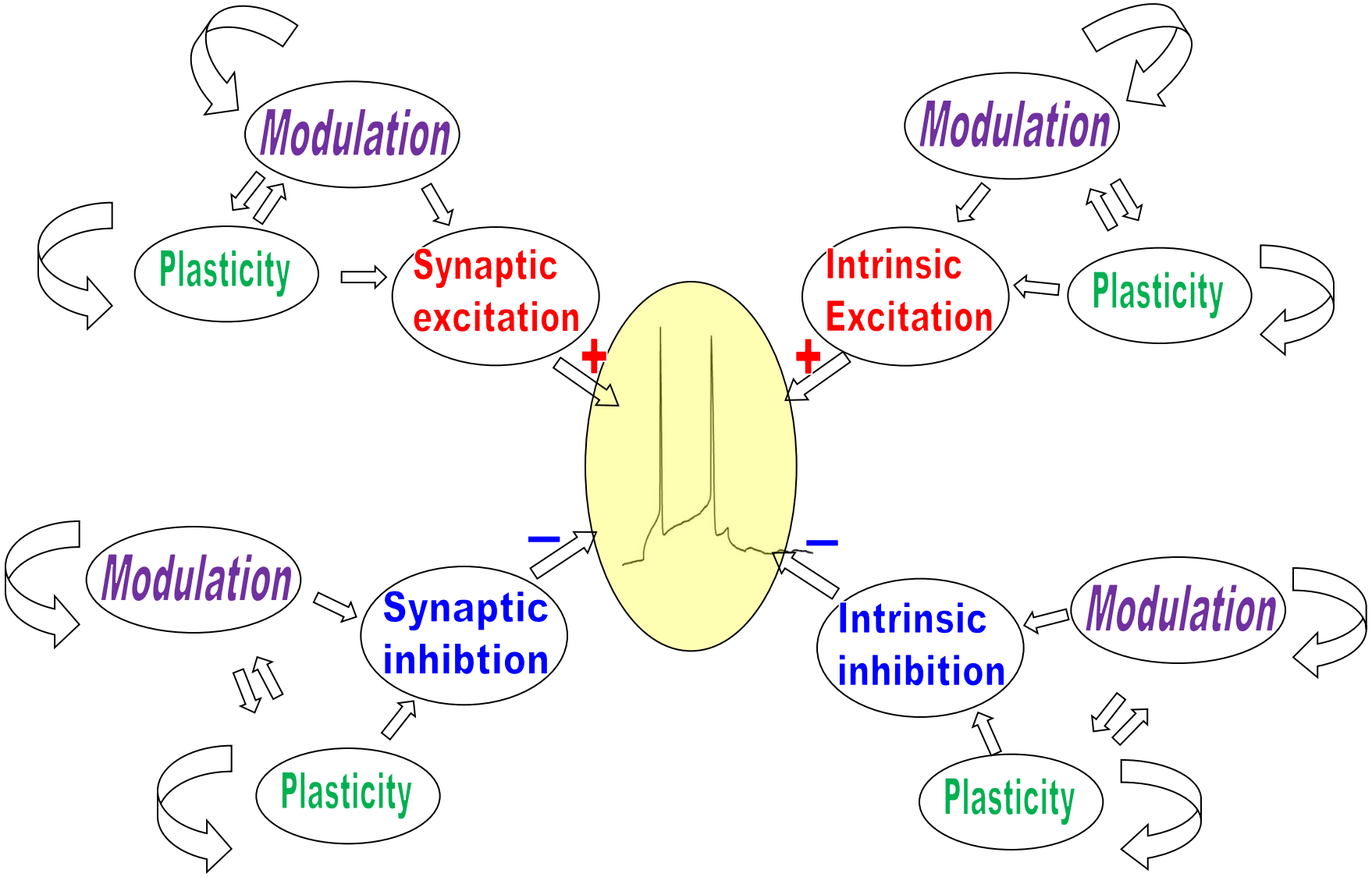
Hormones
Cortisol, Estrogen, Progersteron, Ghrelin, Insulin Vasopressin, AF…

Gliotransmitters
Glu
ATP → Adenosine
D-serine, Taurine
Lactate

Neurotransmitters
Glu via mGluRs
GABA via $GABA_BRs$

Cytokines, Chemokines
TNFα
IL-1β….

Modulation and Plasticity of Excitability



Long-term synaptic plasticity (min – years); LTP and LTD