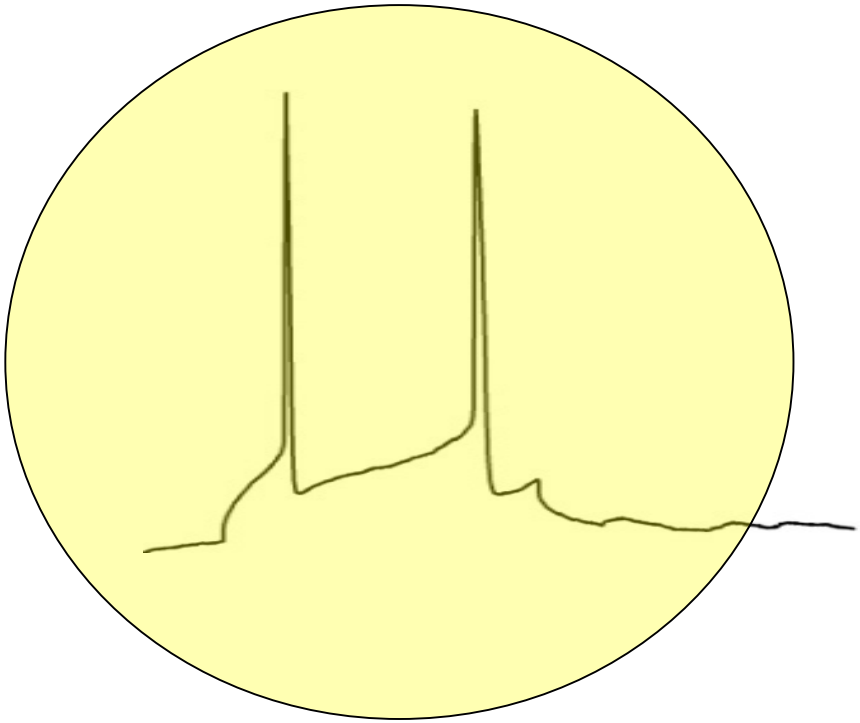
Nervcellsfysiologi

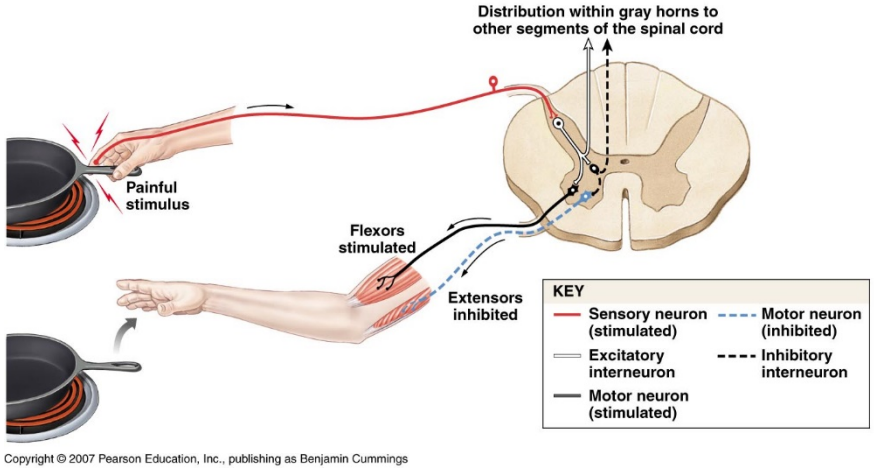


Textbooks:
Bear kap:3-6, 23, 25
Purves kap:2-8; 22-25

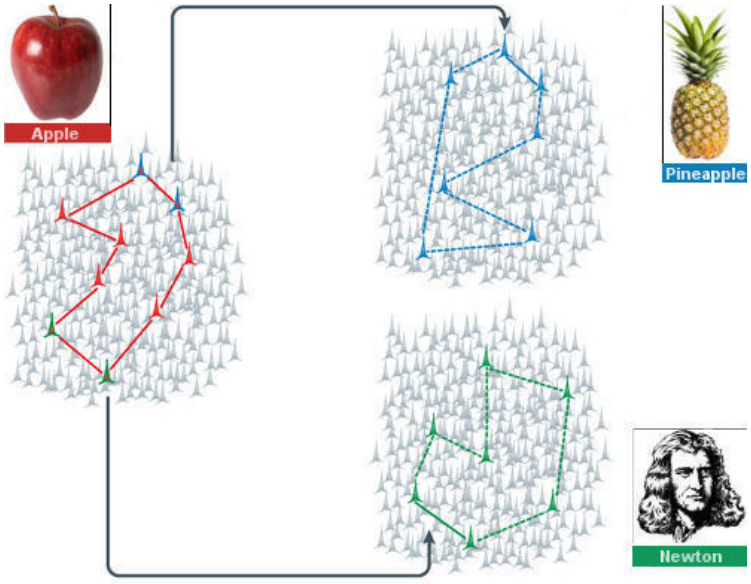
Block 2
Nervcellsfysiologi
Eric Hanse

Action potentials ”in action”

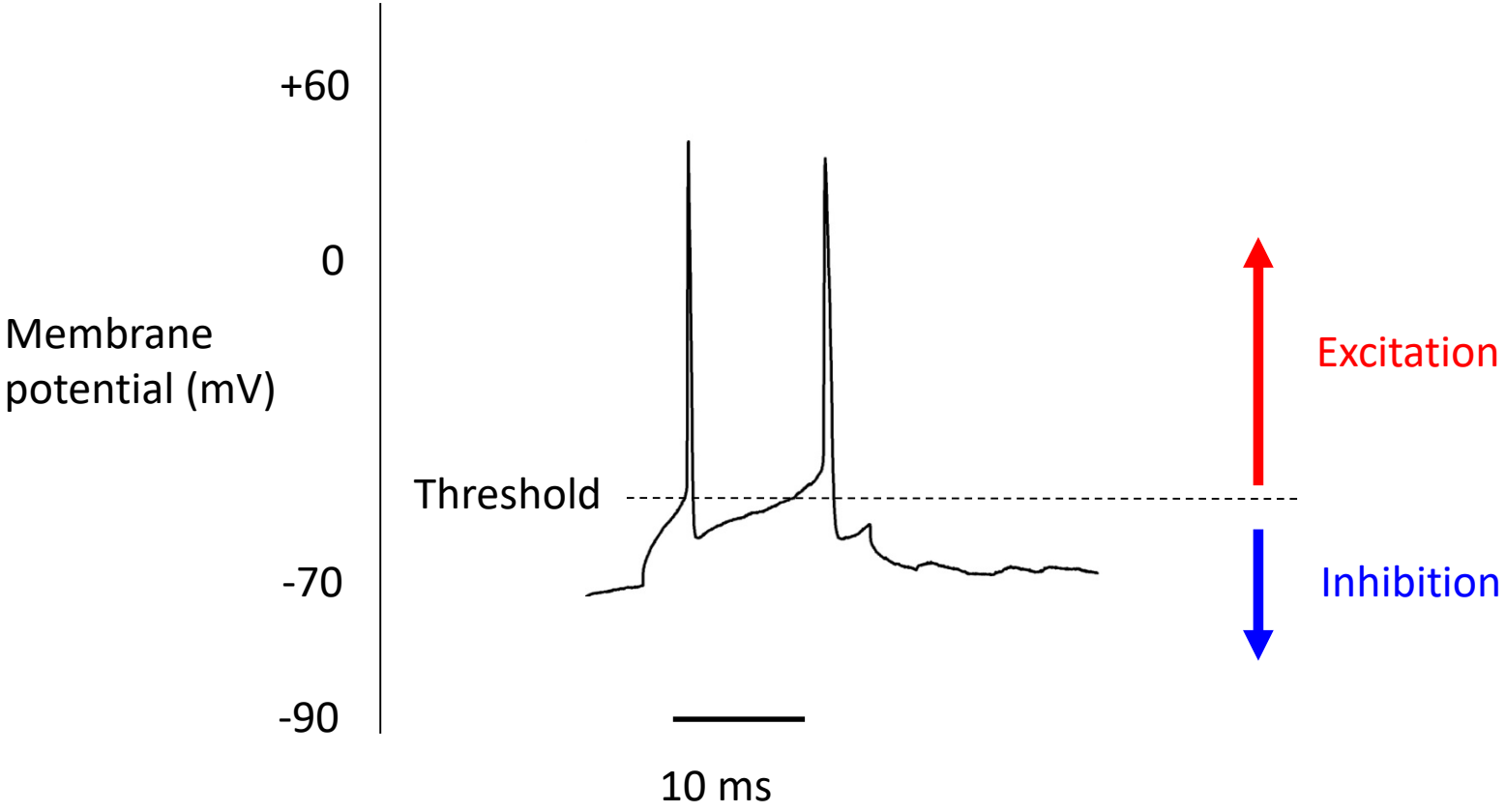
The withdrawal reflex



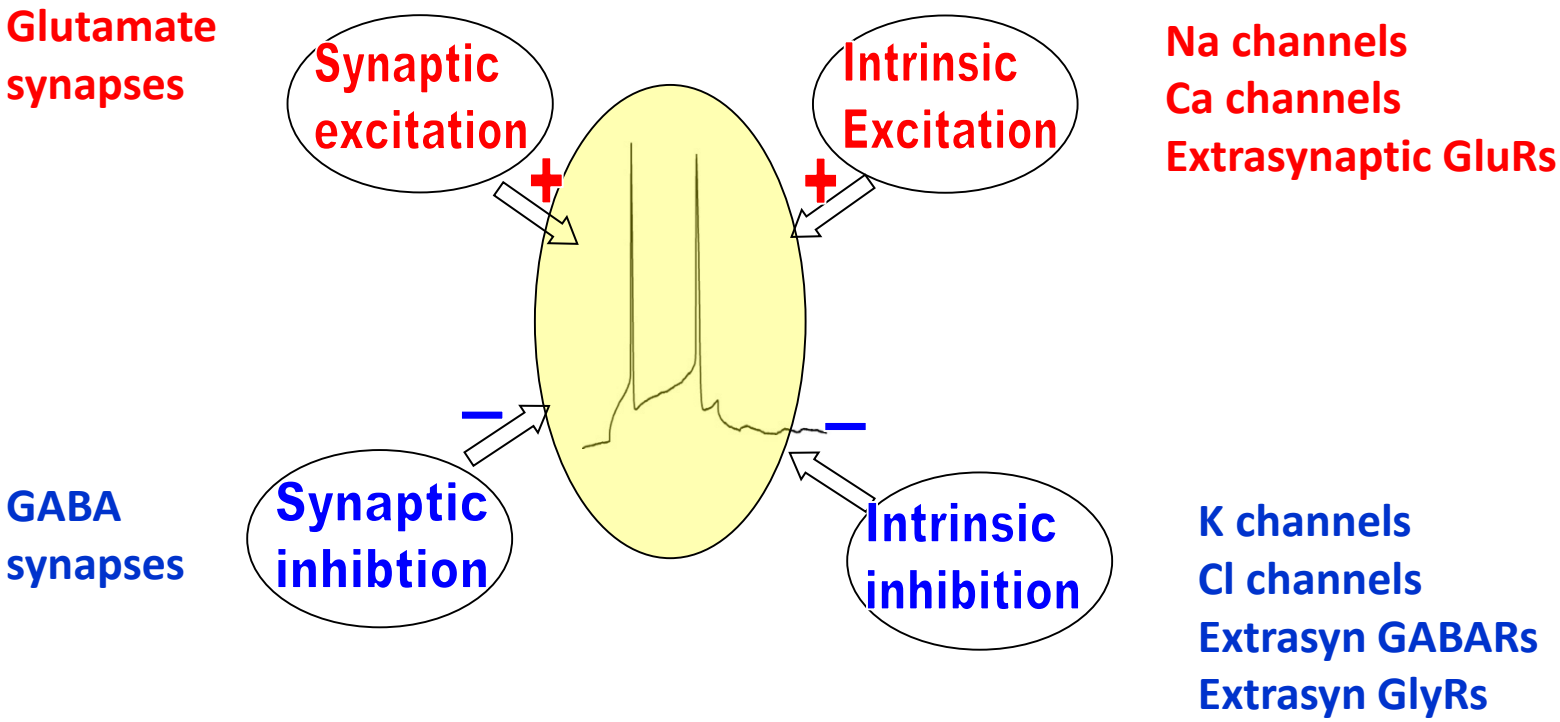
Functional cell assemblies, or engrams



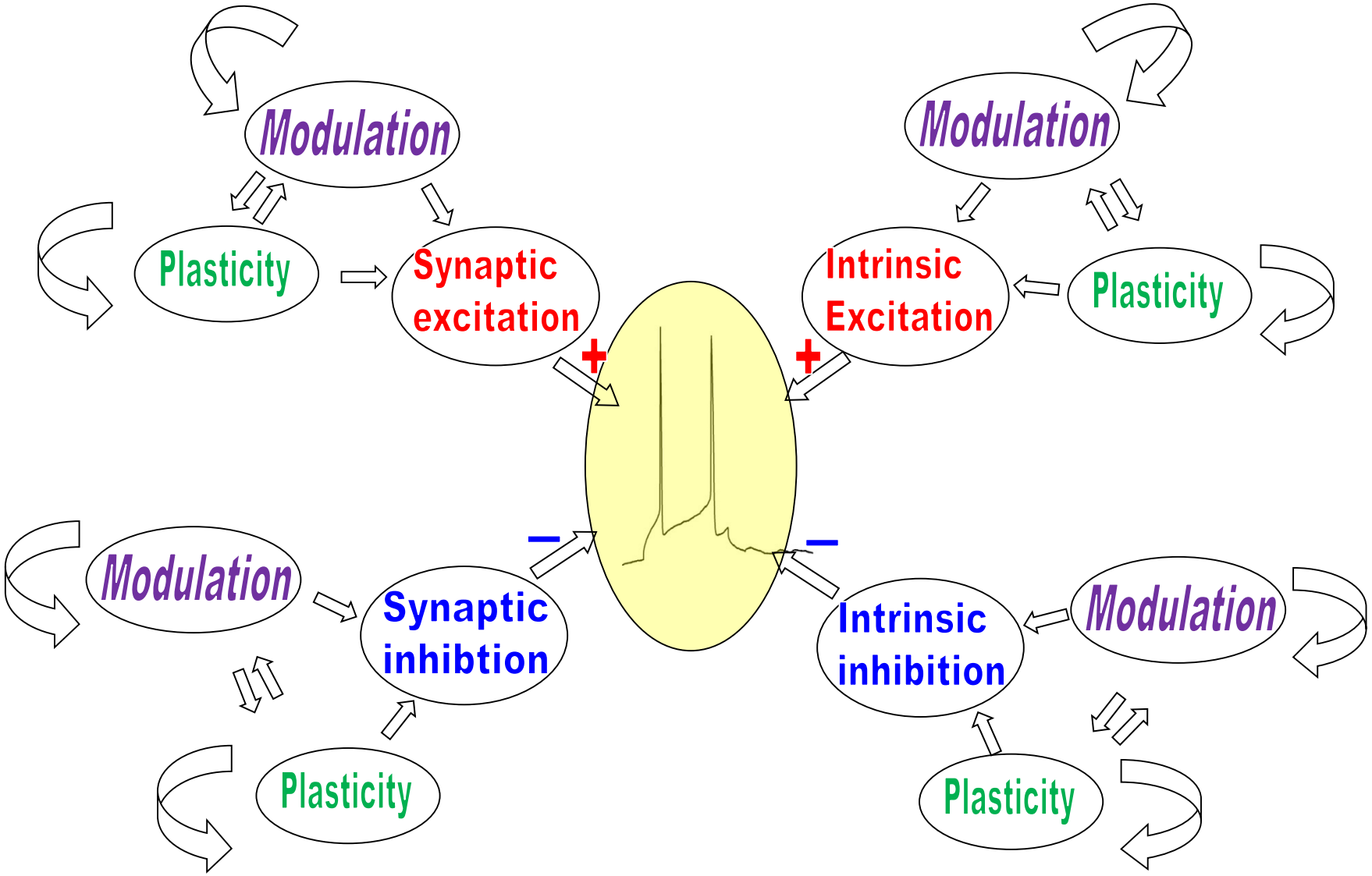
Excitability
– the likelihood of evoking action potentials



Synaptic and Intrinsic Excitability

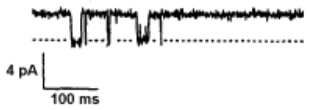


Modulation and Plasticity of Excitability



Electrophysiology – different levels of reductionism

Single protein



Isolated cells

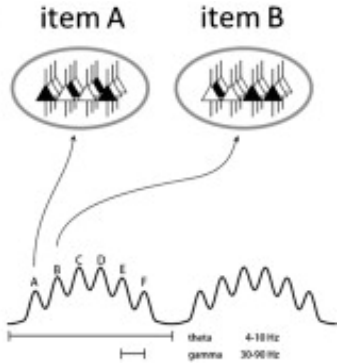
Single synapse

Cell cultures

Single cell

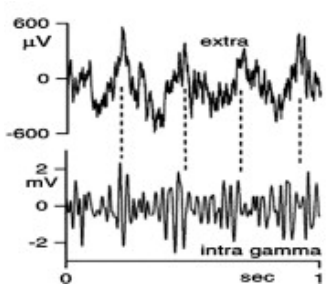
Brain slices

Cell assemblies



In vivo

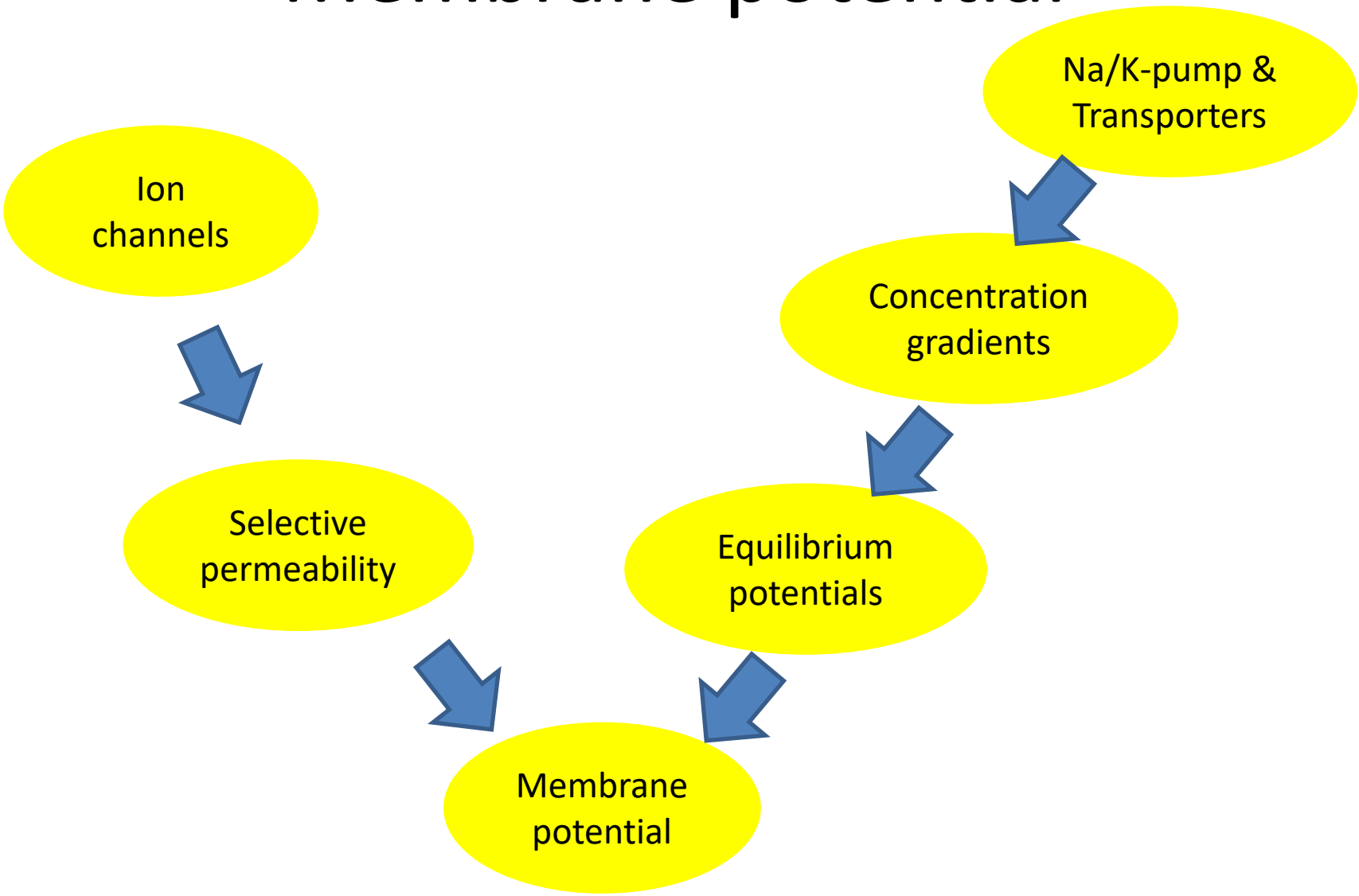
Network oscillations



Patch-clamp recordings

Extracellular recordings

Membrane potential



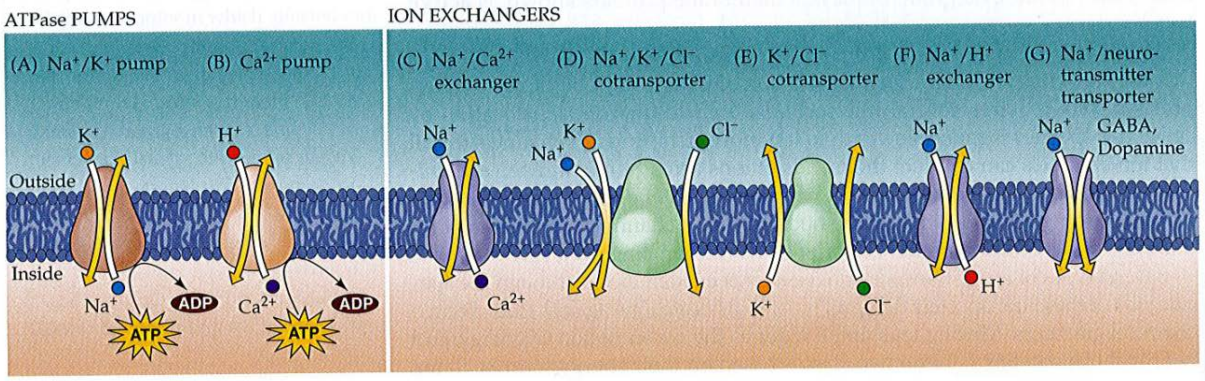
Pumps, concentration differences and equilibrium potential

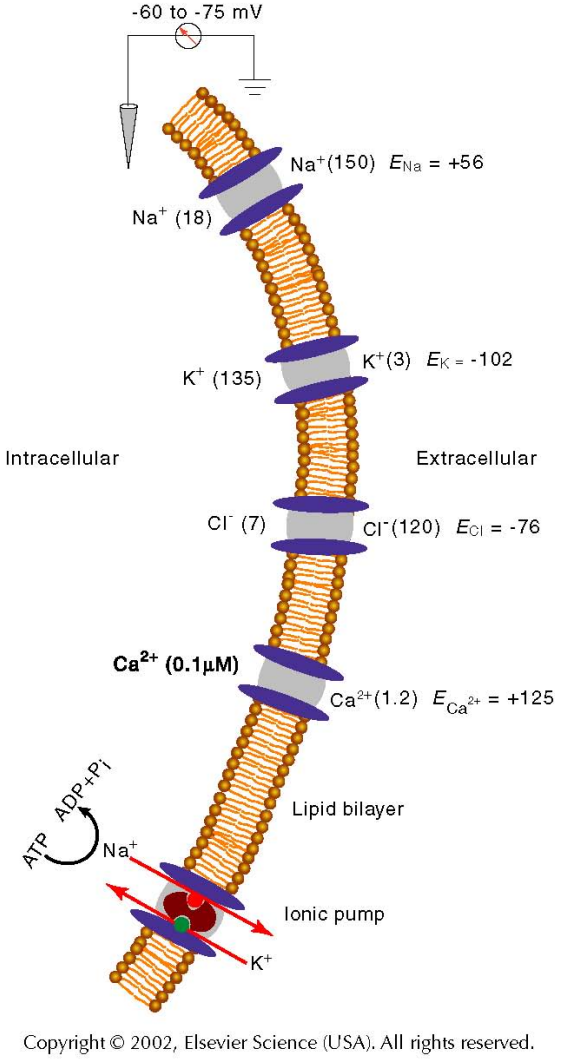
Nernst equation

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

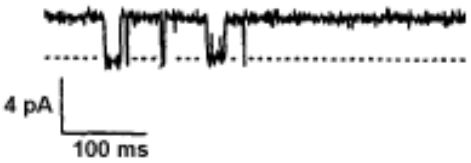
$E_{jon} = 61.54\ \log([jon]_u/[jon]_i)$

The Na/K-pump pumps 2 K^+ in and 3 Na^+ out of the cell.

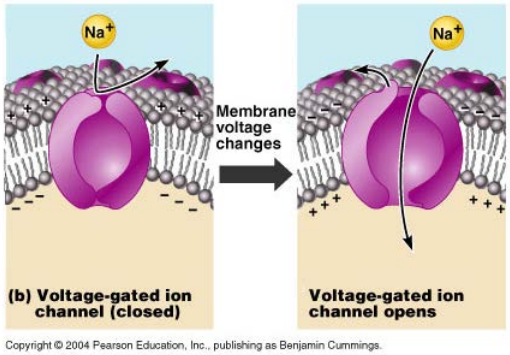


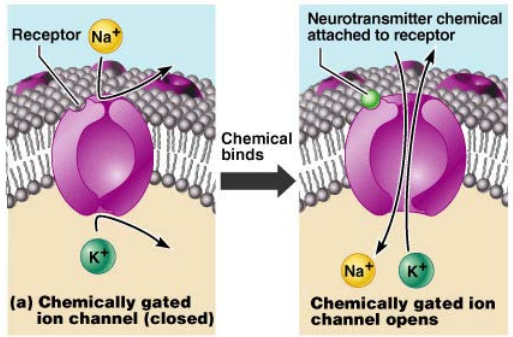


Ion channels

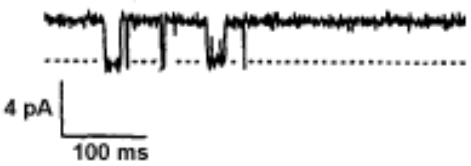


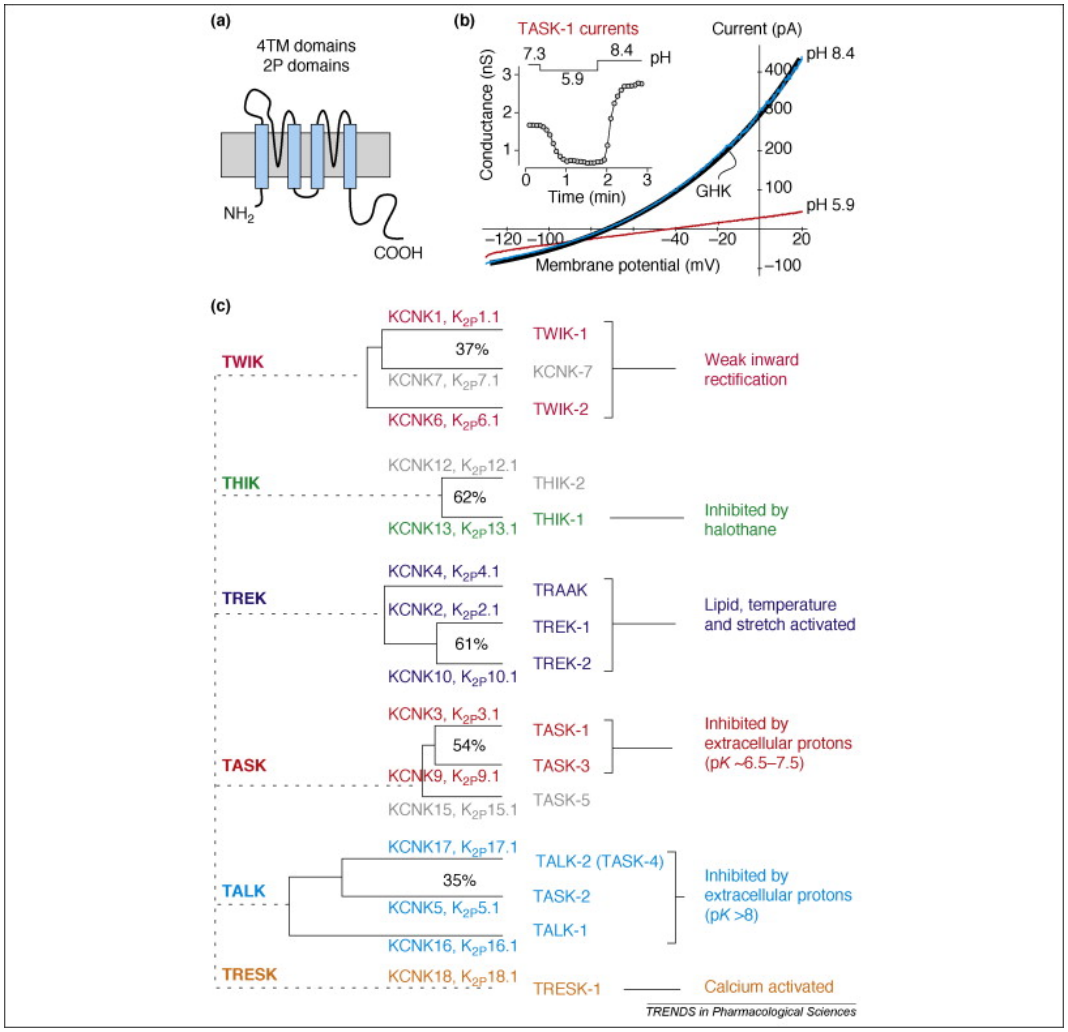
		Gating						
Selectivity		Voltage	Ligand	Ca^{2+}, cAMP, cGMP	Temp	Mech	H	"leak"
	Na							
	K							
	N/K							
	N/K/Ca							
	Ca^{2+}							
	Cl/HCO_3							





Leak channels





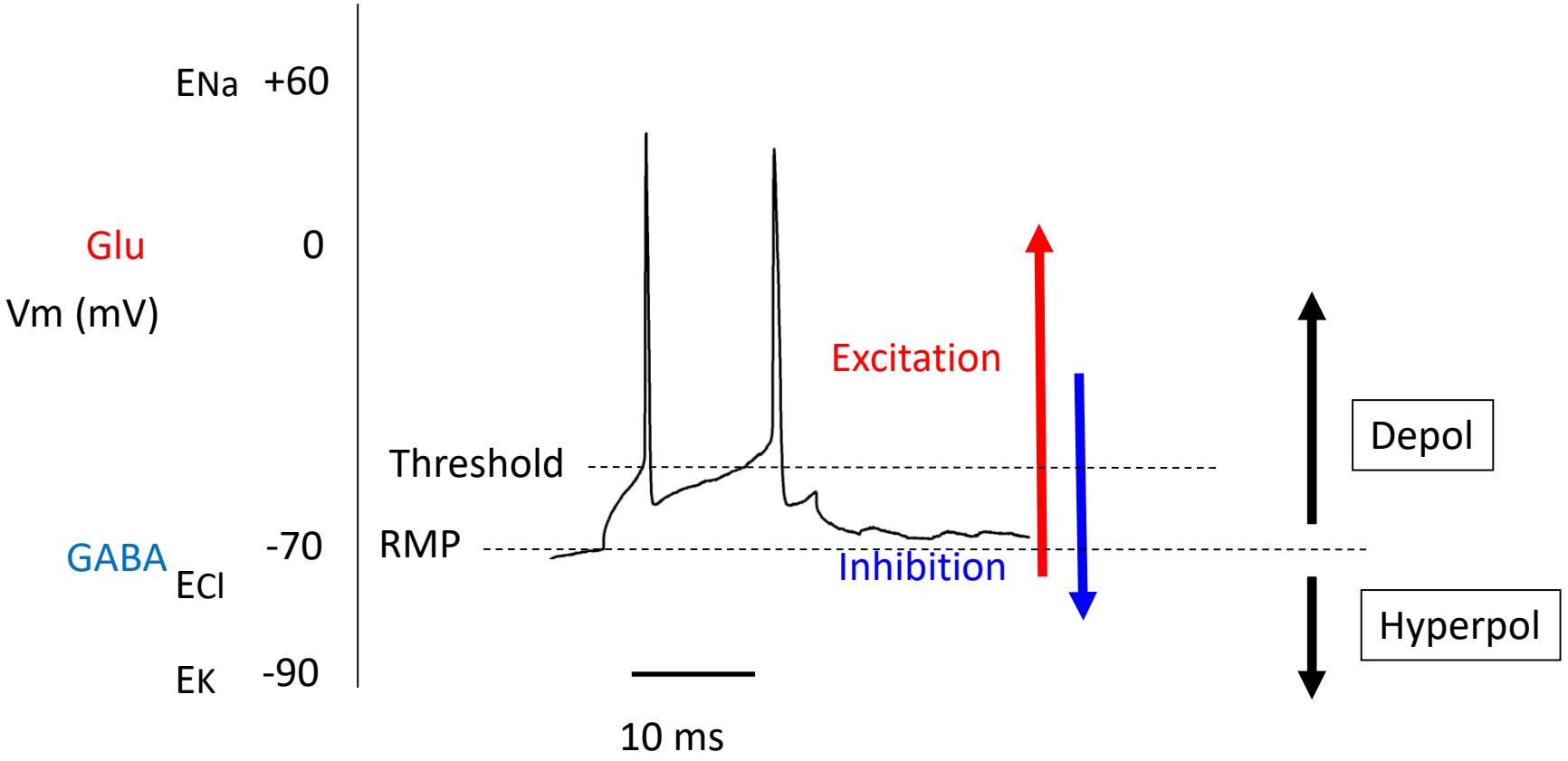
The resting permeability for K^+ is much higher than for Na^+, but the driving force (at resting membrane potential) is much higher for Na^+ than for K^+. The resultant currents for K^+ and Na^+ are therefore equal

The Sodium "Leak" Has Finally Been Plugged

Neuron *54*, May 24, 2007

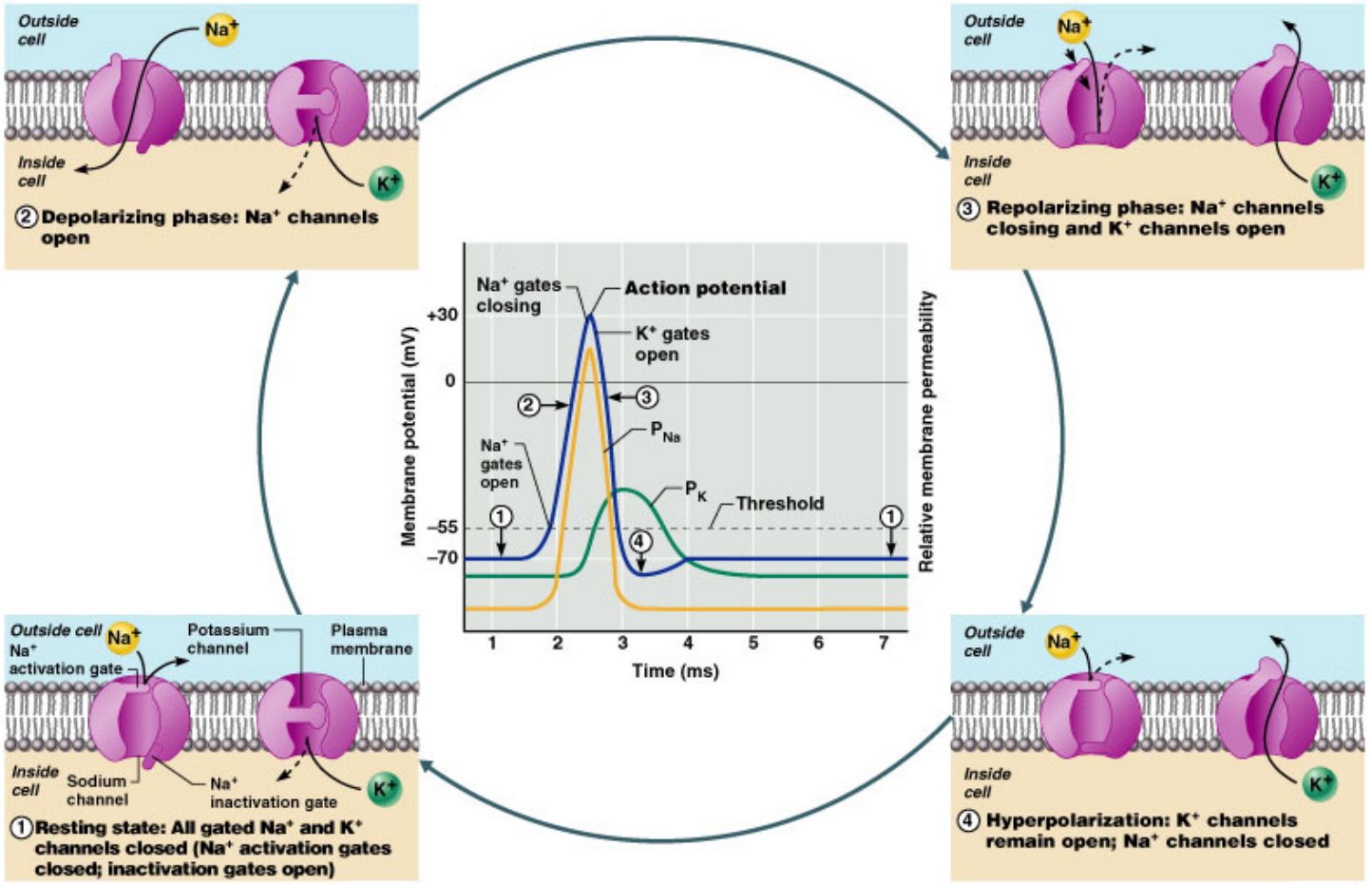
Trends in Pharmacological Sciences (2008) 29:11

Membrane potential

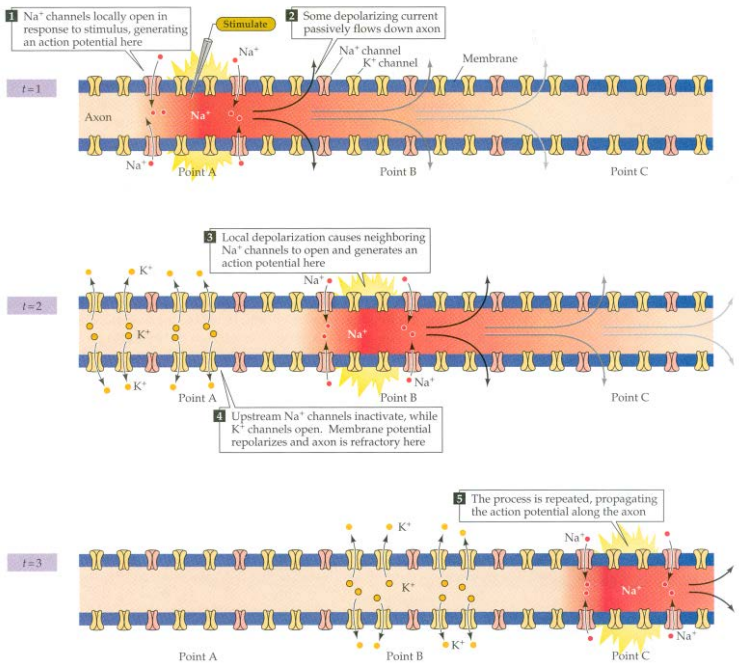


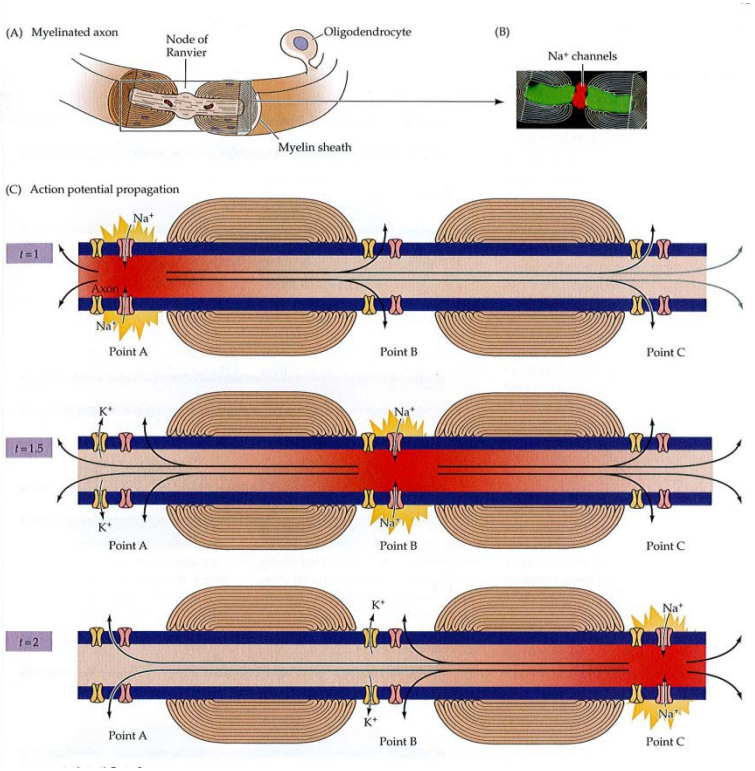
The Goldman equation $V_m = 61.54 \text{ mV} \log \frac{P_K [K^+]_u + P_{Na}[Na^+]_u}{P_K [K^+]_i + P_{Na}[Na^+]_i}$

Action potential – ”all-or-none”



Propagation of the action potential

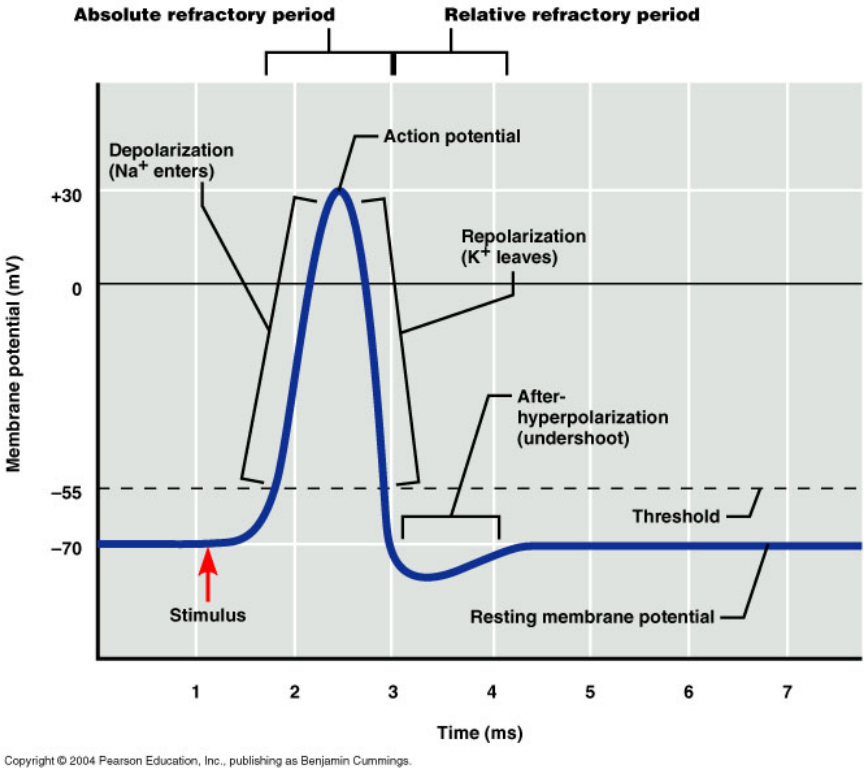




Myelin
Diameter
Temperatur

	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

Refractory period following the action potential



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

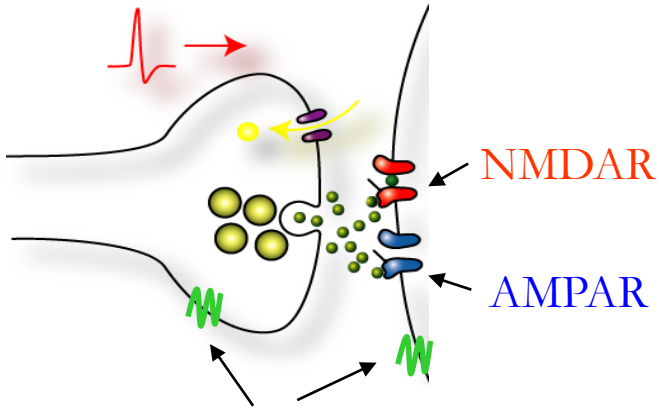
Relative refractory period = Voltage-gated Na^+-channels de-inactivates during this period and the membrane potential is hyperpolarized. A stronger than normal depol is required to evoke an action potential.

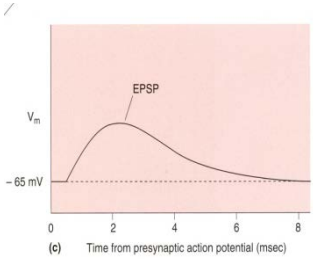
Optical recording of the action potential

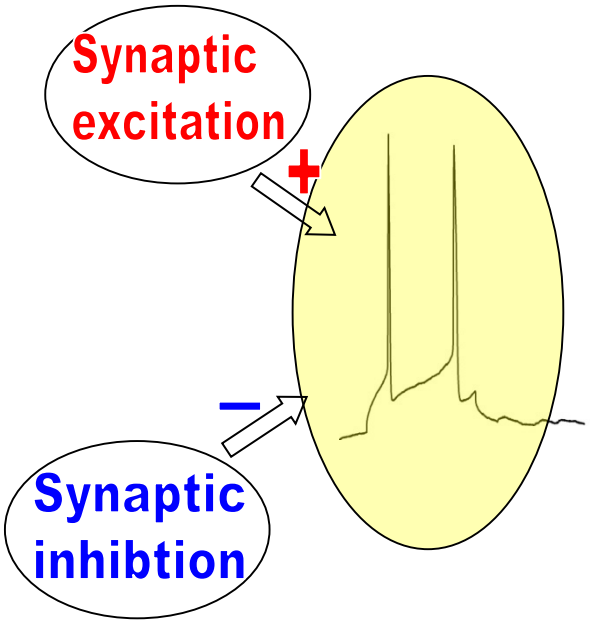
Hochbaum et al (2014) **All-optical electrophysiology in mammalian neurons using engineered microbial rhodopsins** *Nature Methods* 11: 825-833

Synaptic excitation and inhibition

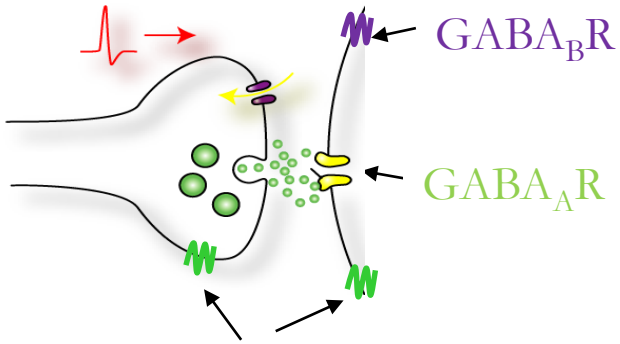
Excitatory synapse

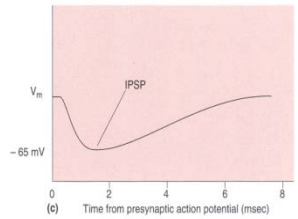




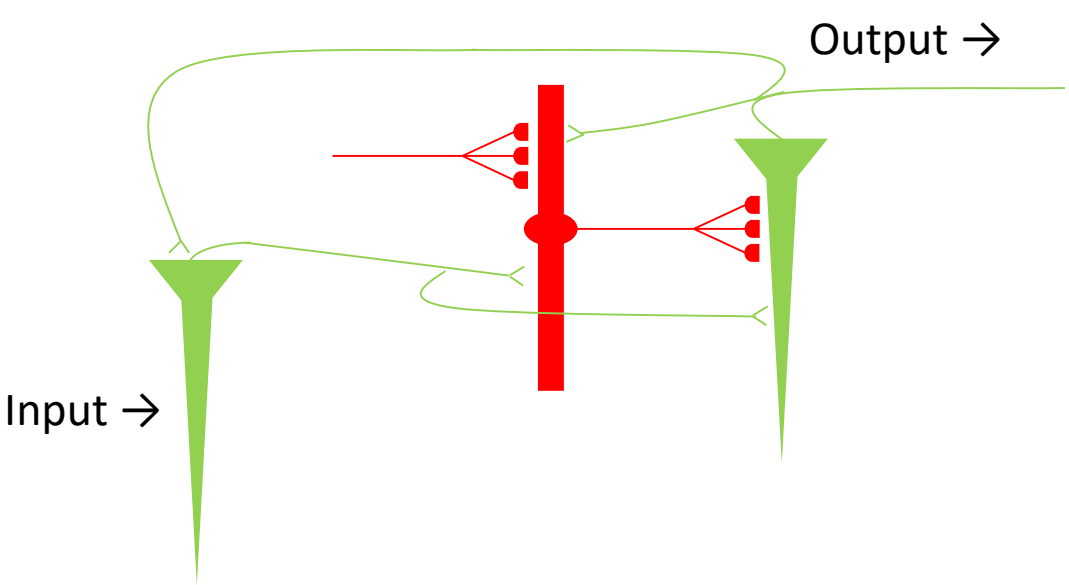


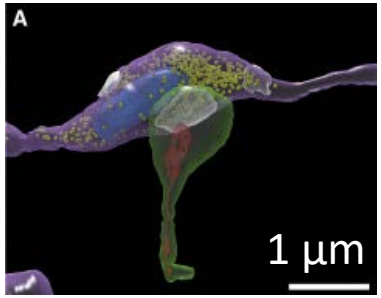
Inhibitory synapse



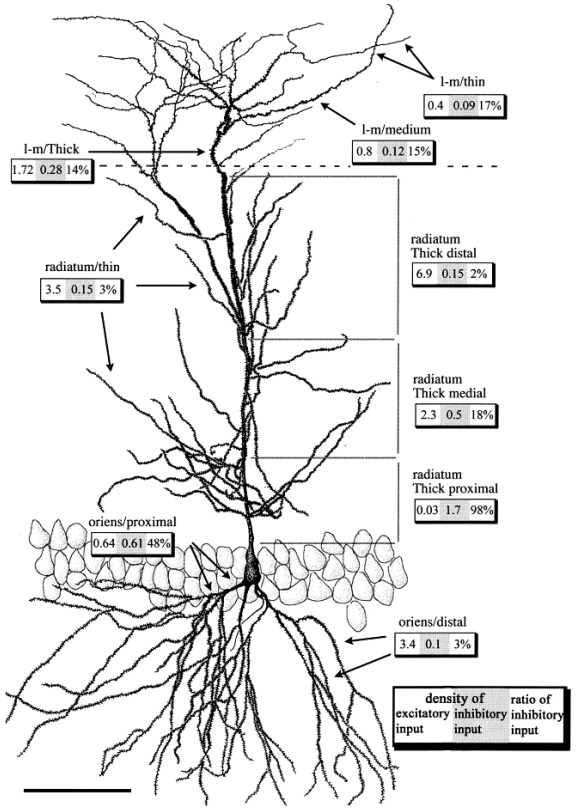


Glu and GABA synapses





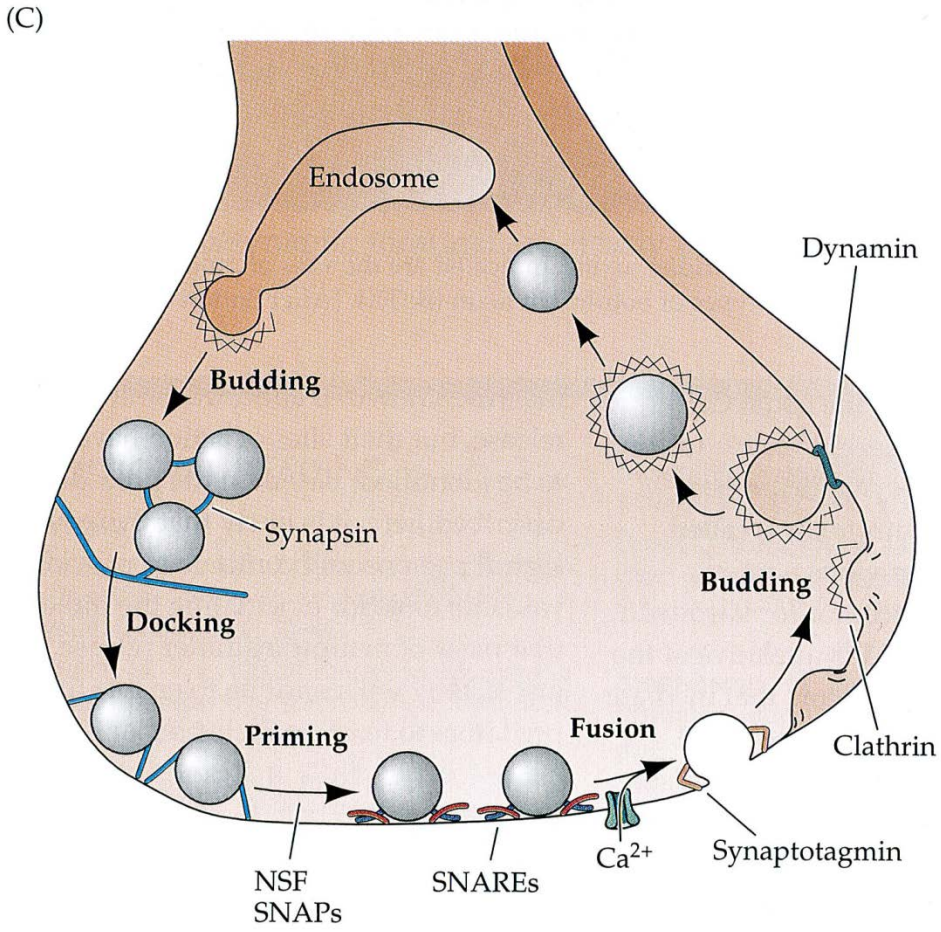
Kasthuri et al (2015) **Saturated reconstruction of a volume of neocortex** Cell 162: 648661



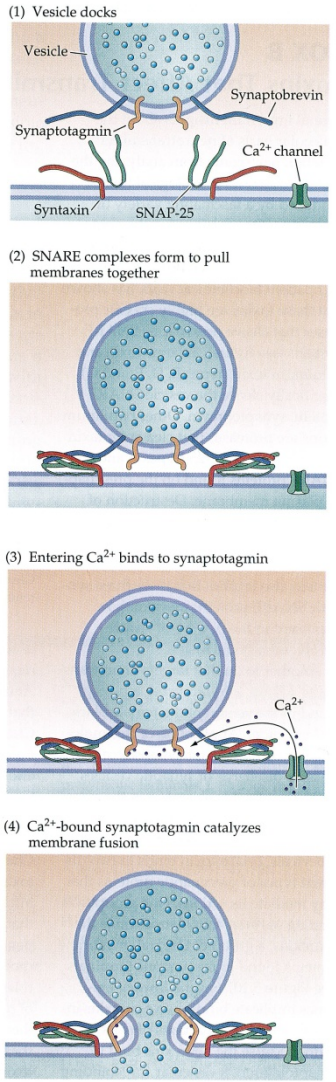
Cortical pyramidal cell:
ca. 30000 Glutamate synapses (90%)
ca. 2000 GABA synapses (10%)

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

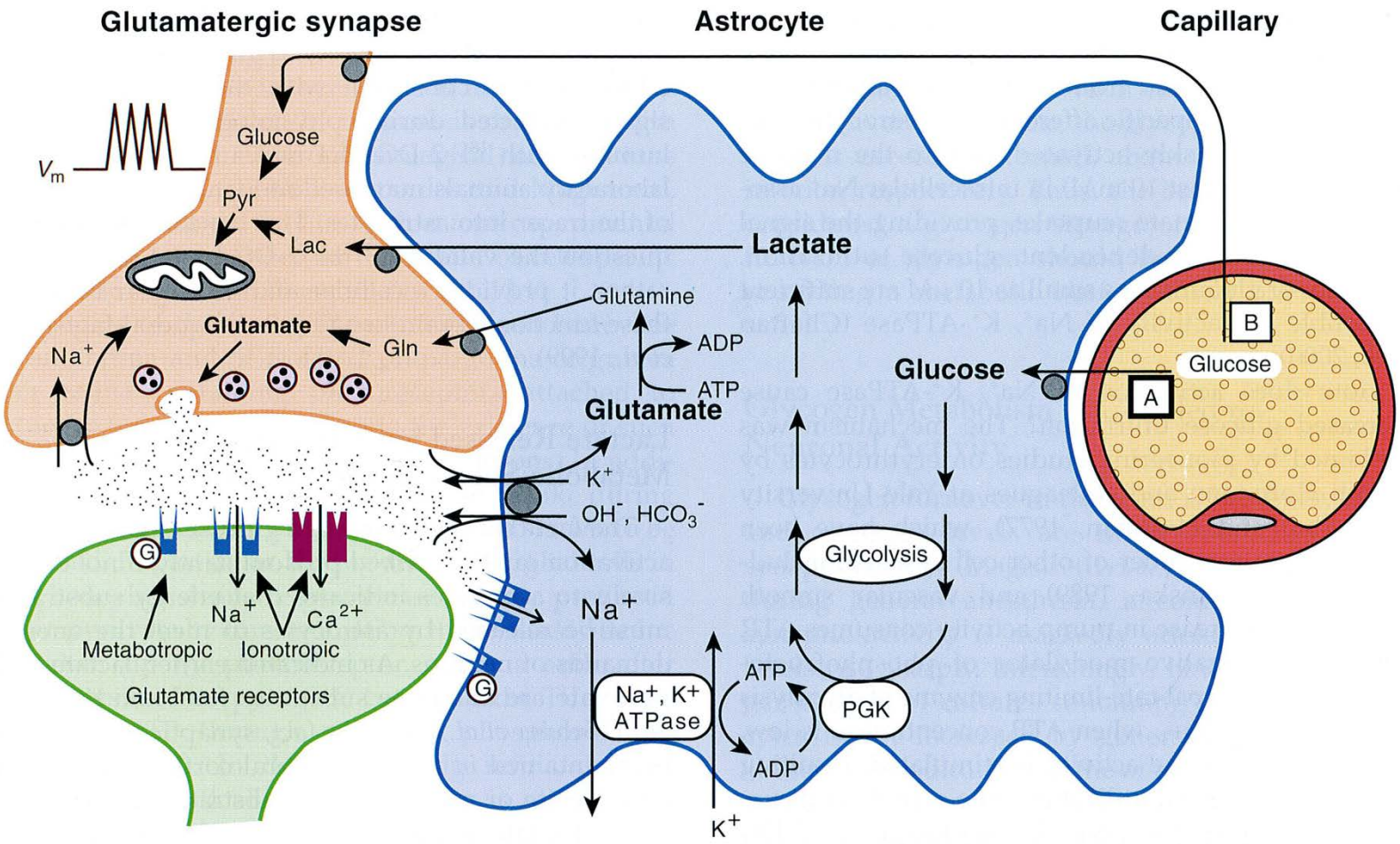
Presynaptic release of transmitter vesicle



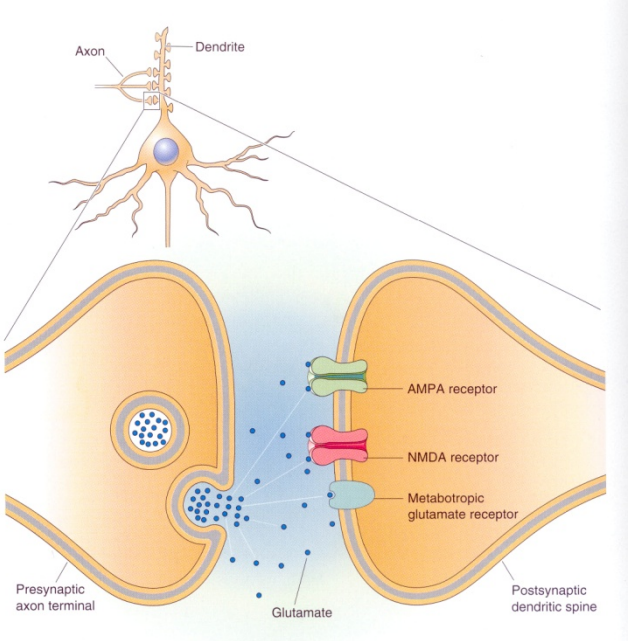
SNARE-mediated exocytosis



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**

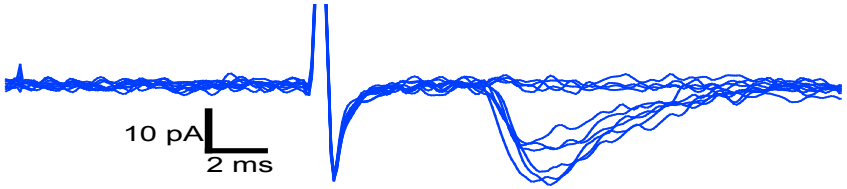
***p* = release probability**

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

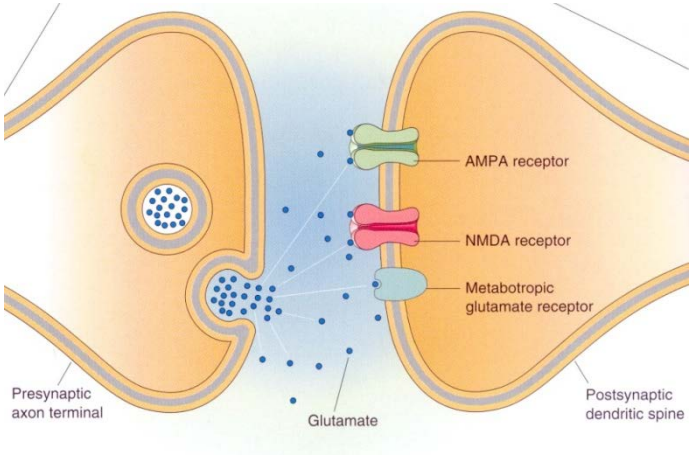
***q* = quantal size**

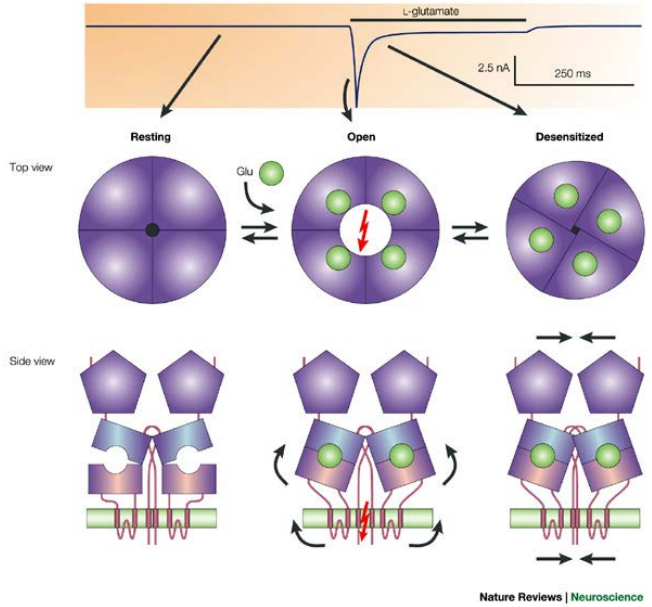
The magnitude of the postsynaptic response to one vesicle

Recording from one synapse



The Glutamate synapse

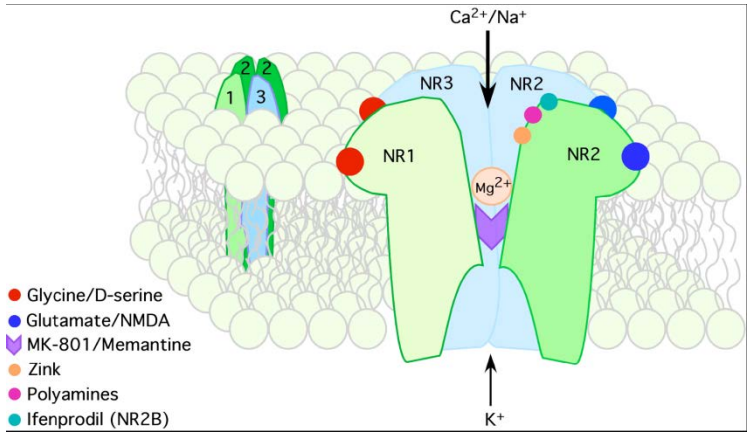




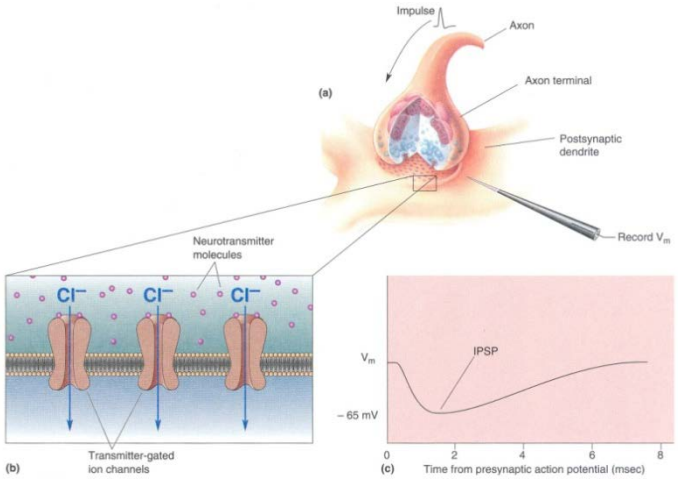
1. The AMPA receptor channel:
-opened by glutamate
-permeates Na^+ and K^+
-gives rise to a brief (ca. 10 ms) EPSP

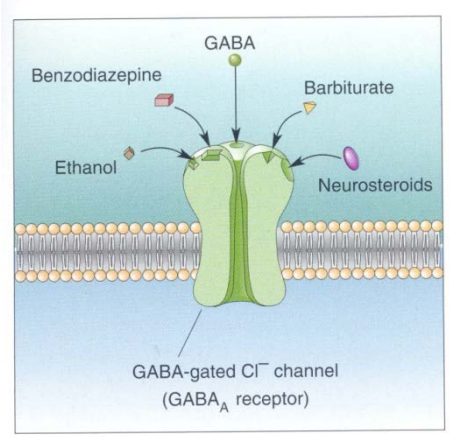
2. The NMDA receptor channel:
-opened by glutamate (and Gly/D-Ser) + depol
-permeates Na^+, K^+ and Ca^{2+}
- gives rise to a brief long-lasting (ca. 100 ms) EPSP
-is necessary for the induction of synaptic plasticity; Long-term potentiation (LTP) och long-term depression (LTD).

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.

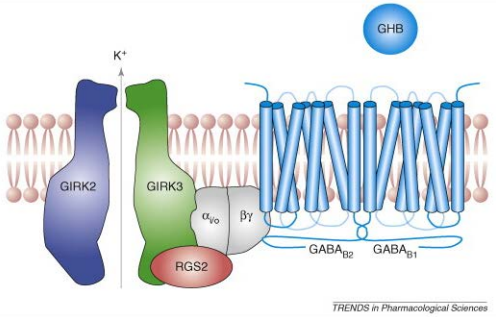


The GABA synapse



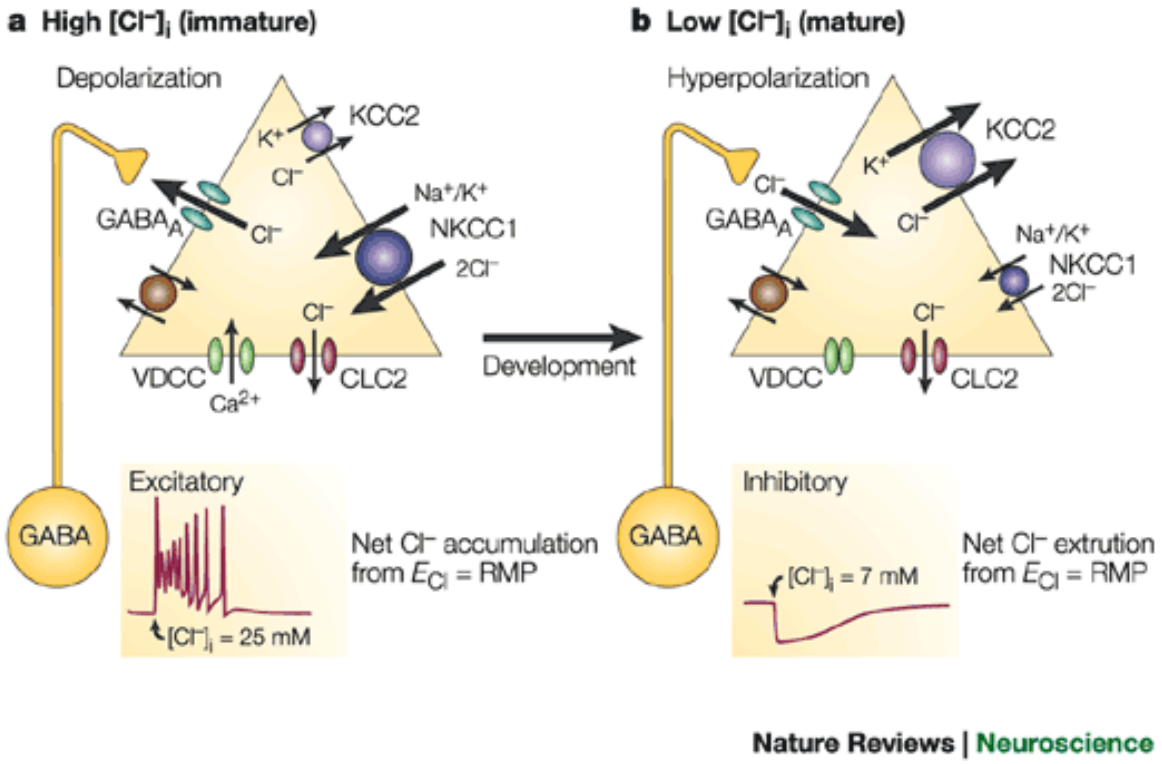


$GABA_A$ Rec

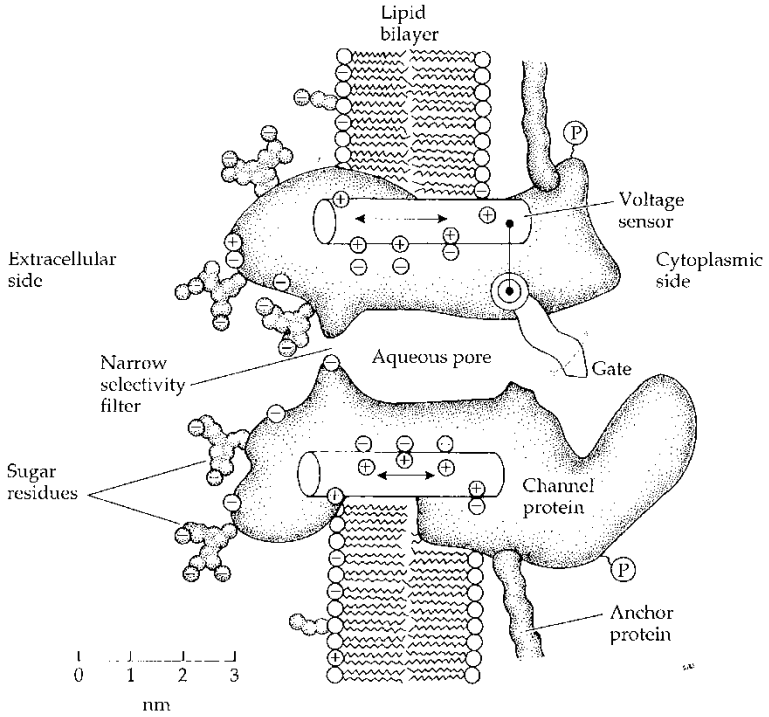


$GABA_B$ Rec

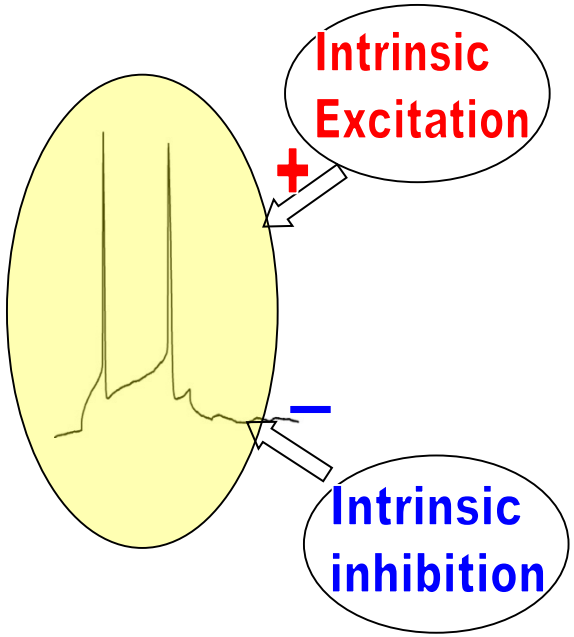
The i.c. Cl^- concentration determines the response of the $GABA_A$ receptor channels



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

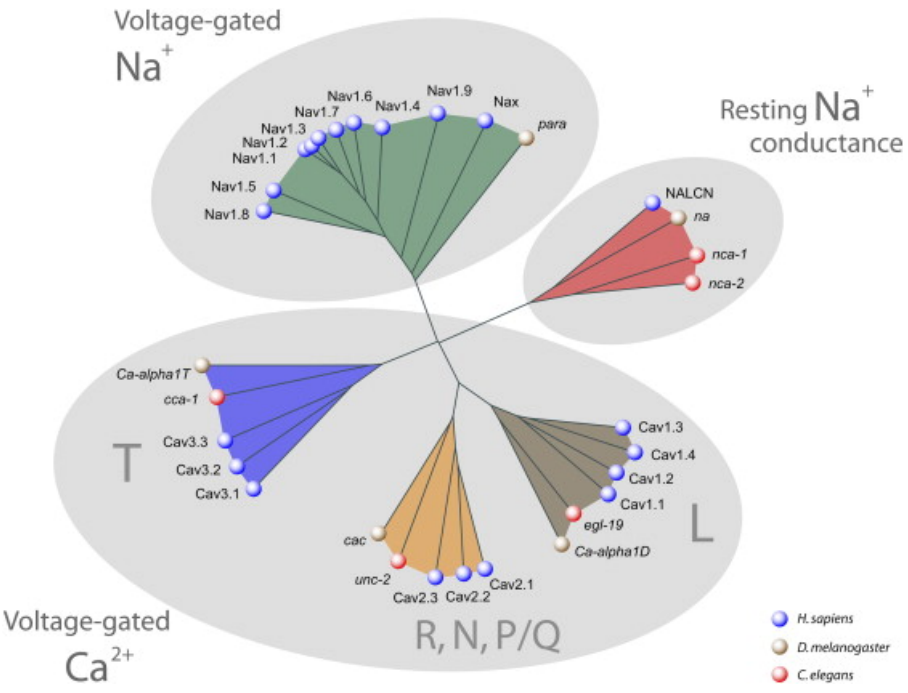


From Hille ”Ion channels in excitable membranes” 3rd ed

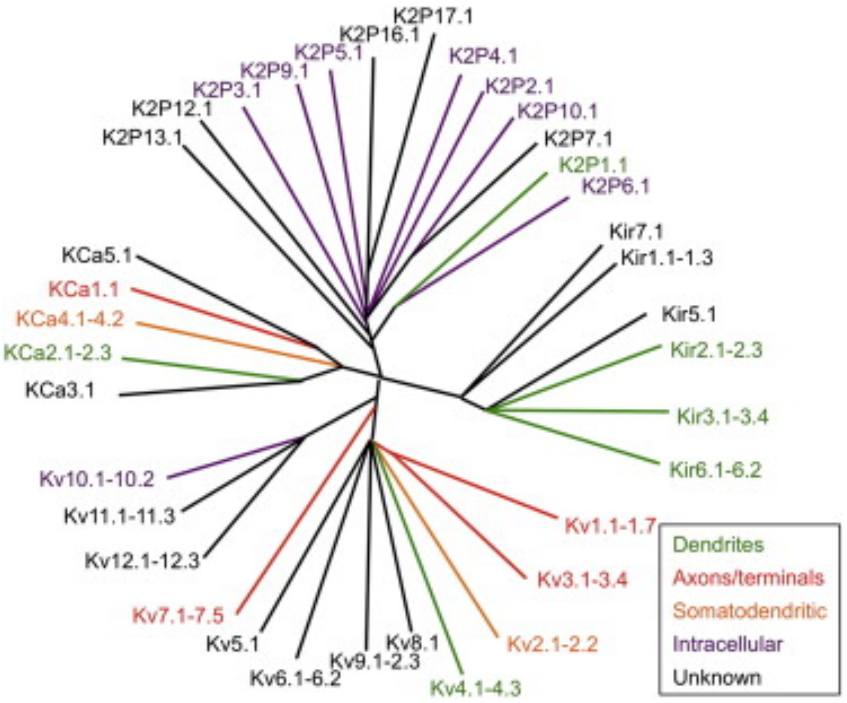


E.c. Calcium

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

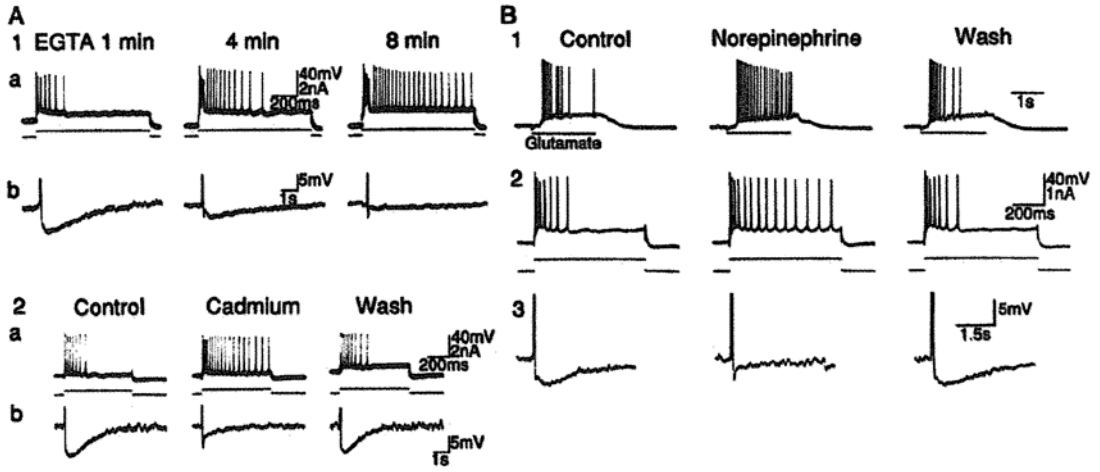


K-channels



Neuron, Volume 85, Issue 2, 2015, 238 - 256

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



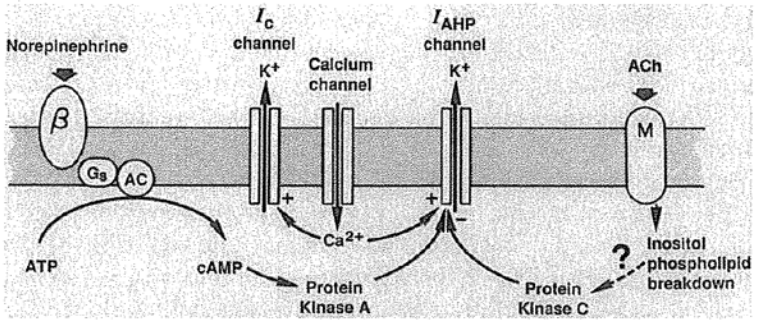
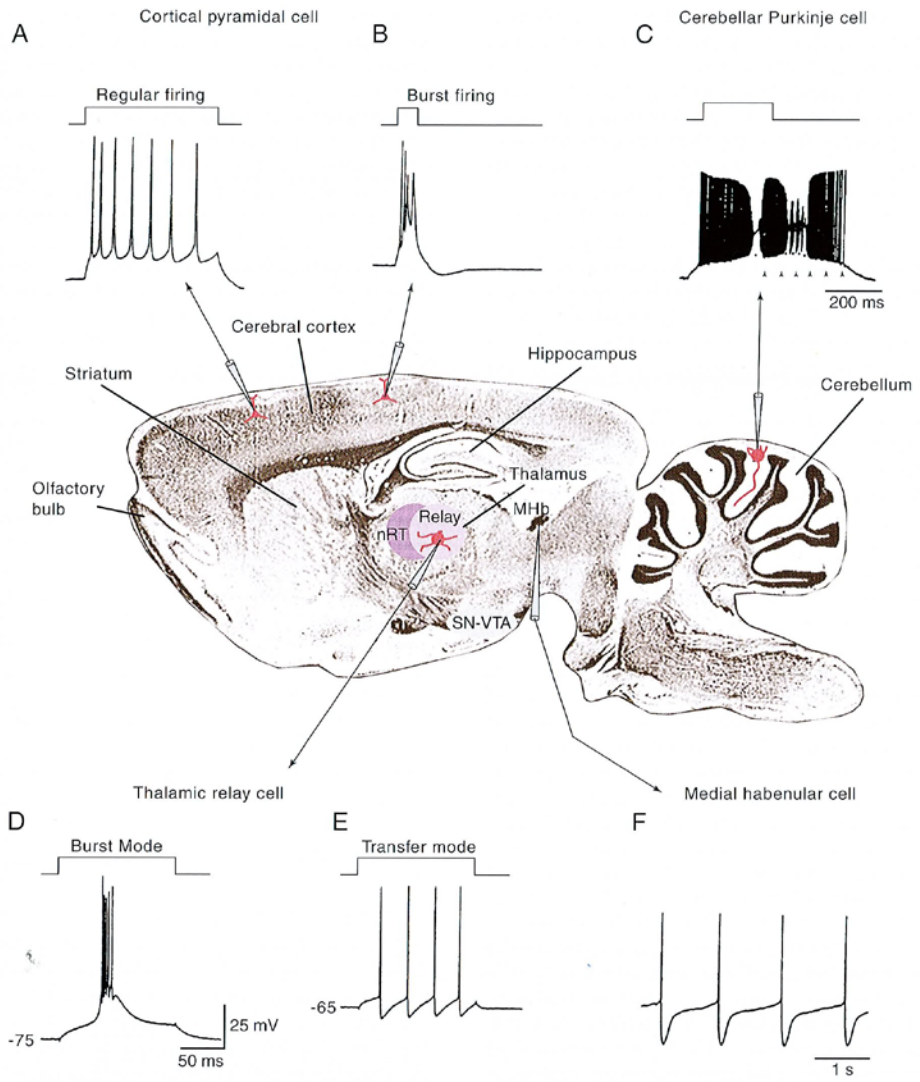


Fig. 2. Diagram of the proposed mechanisms of action of norepinephrine and acetylcholine in blocking the slow Ca^{2+}-activated K^+ conductance.

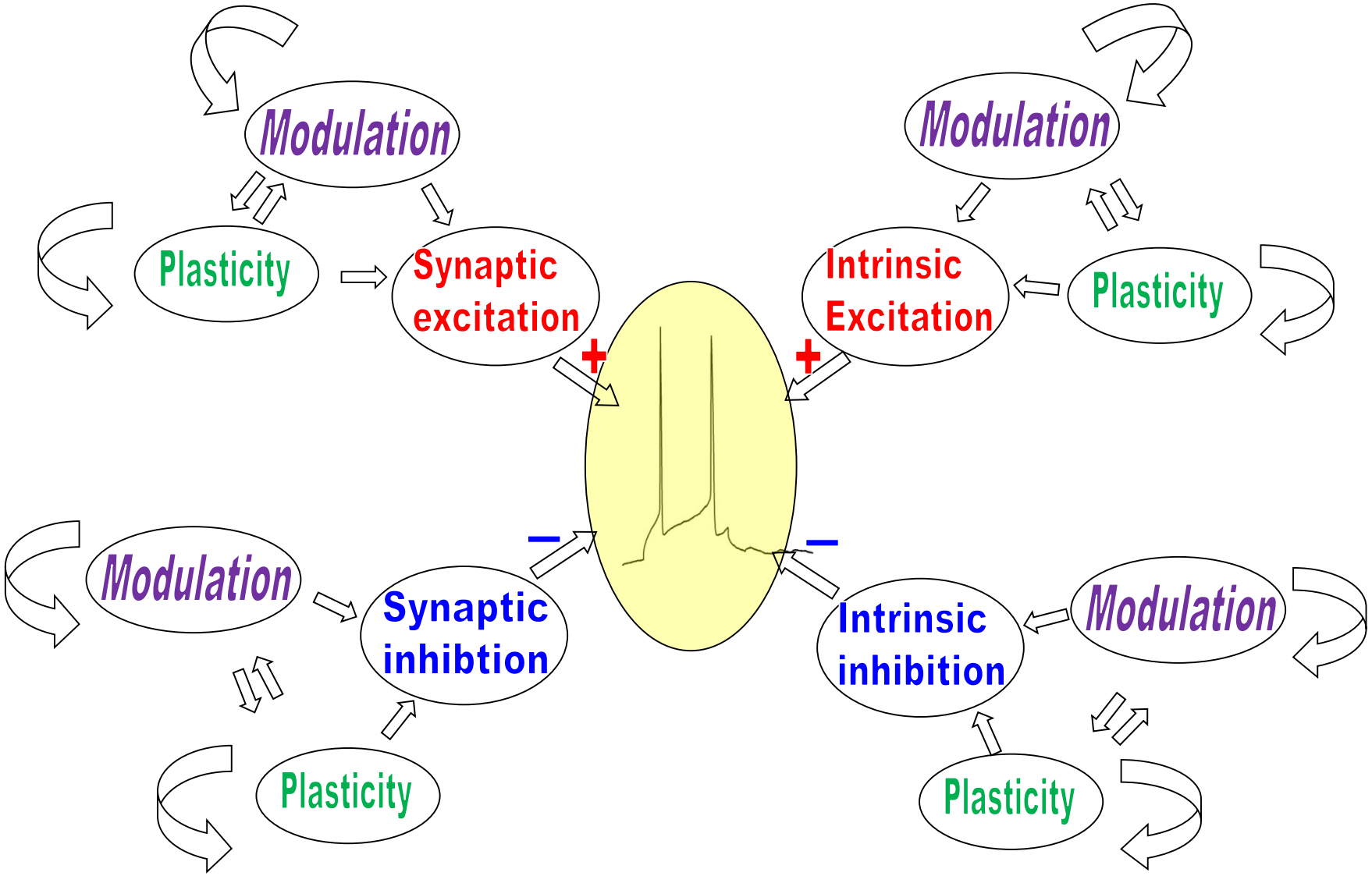
Nicoll, RA

SCIENCE, VOL. 241

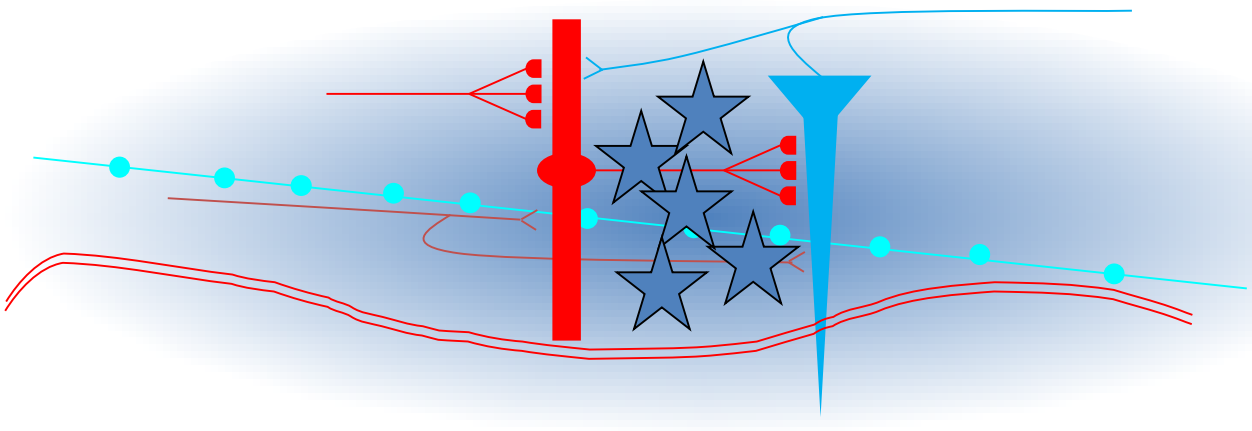
Different firing patterns because of differences in intrinsic excitability



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

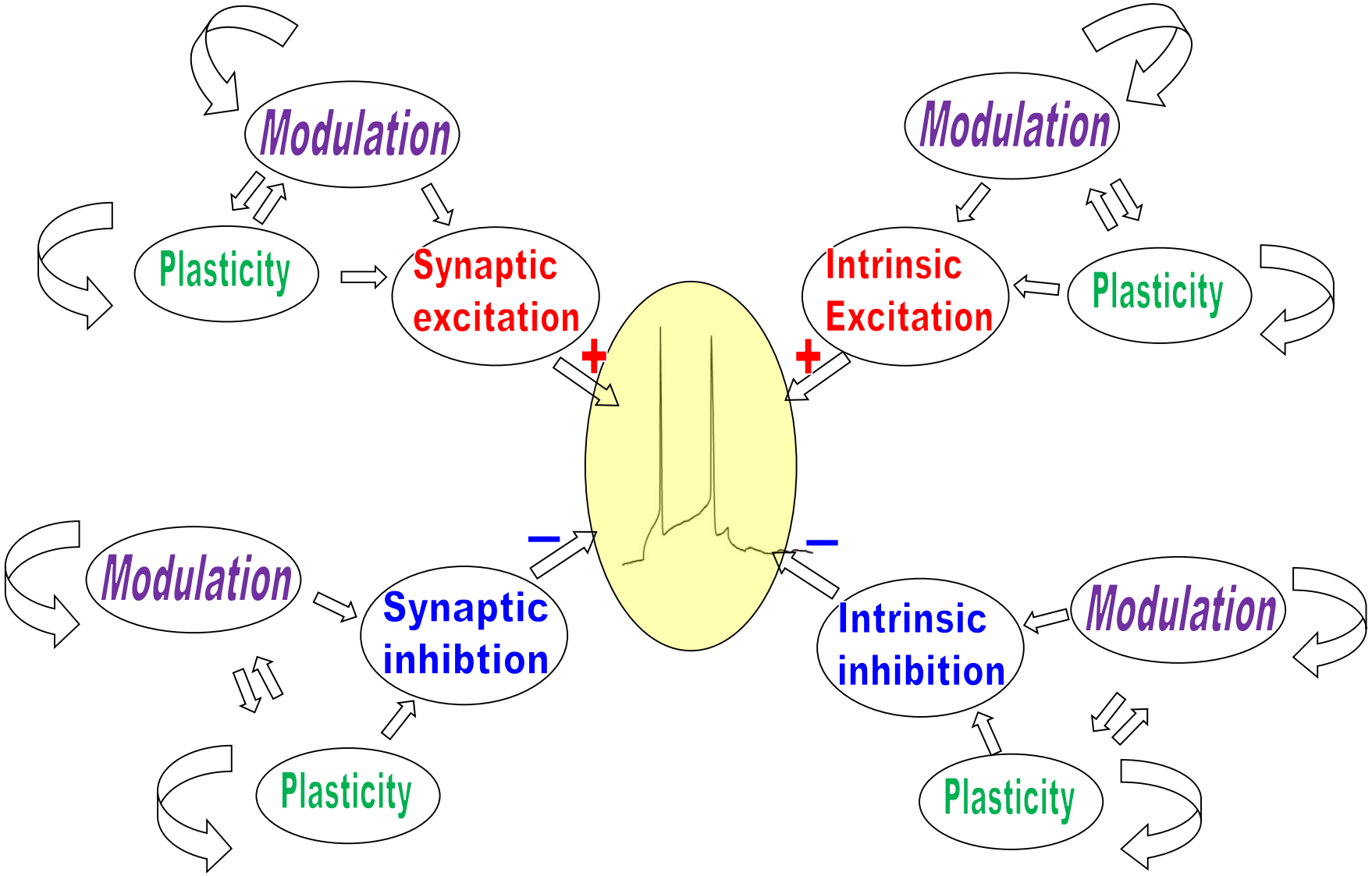
Hormones
Cortisol, Estrogen, Progersteron, Ghrelin, Insulin Vasopressin, AF…

Gliotransmitters
Glu
ATP → Adenosine
D-serine, Taurine

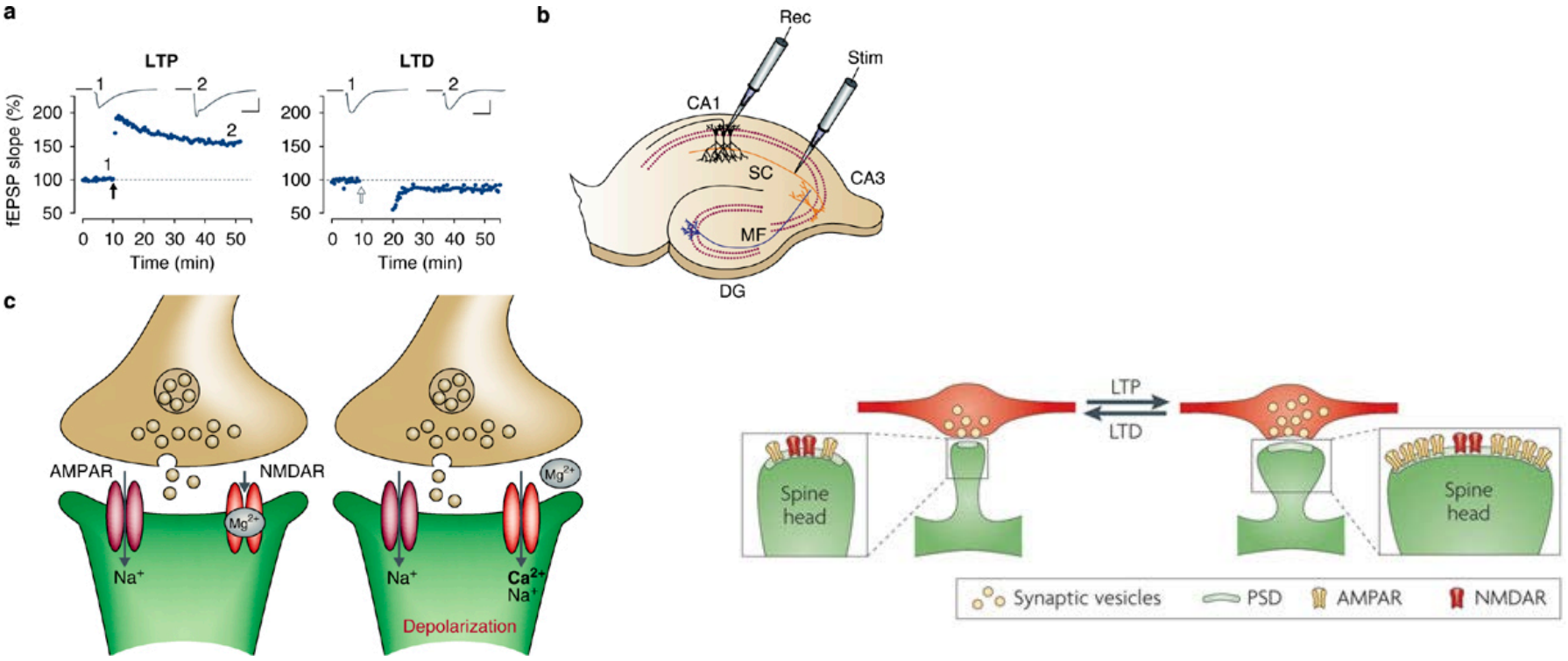
Neurotransmitters
Glu via mGluRs
GABA via $GABA_BRs$

Cytokines, Chemokines
TNFα
IL-1β….

Modulation and Plasticity of Excitability



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



Modulation and Plasticity of Excitability