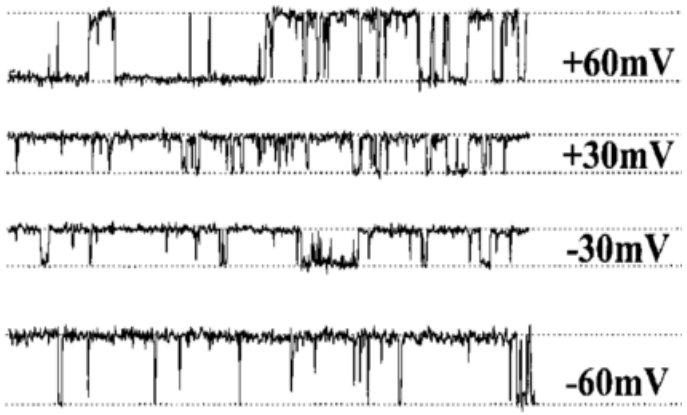
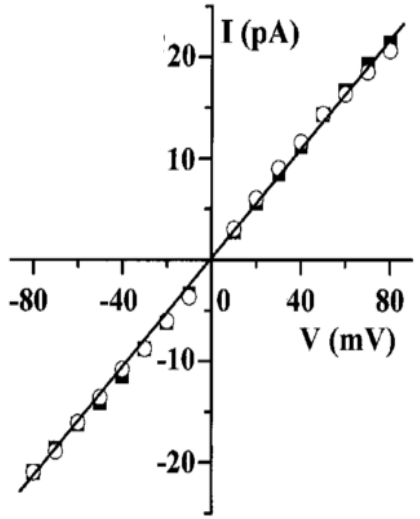
Permeability is a measure of how easily ions can move across a membrane, regardless of whether they are moving or not. Conductance is a measure of how much charge actually moves across the membrane.





$G = 1 / R$

$I = G \times V$

Conductance is proportional to permeability

Na_v and Ca_v kissing-cousin ion channels

25 % identical in AA sequence in their conserved transmembrane domains

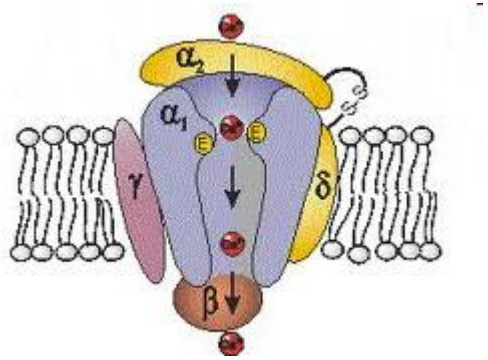
Nav channels initiate and conduct action potentials in nerve and muscle

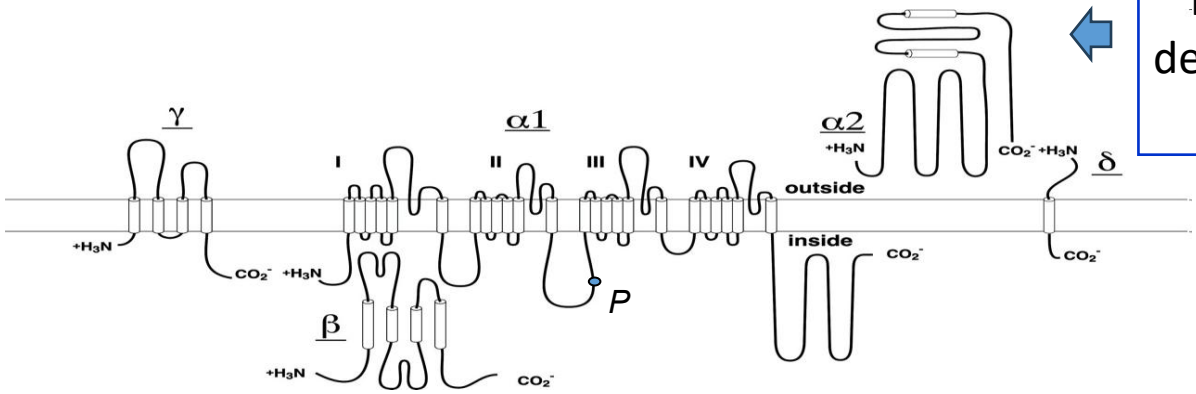
Voltage-gated Ca^{2+} channels (Ca_v)

- They initiate numerous physiological processes:

- contraction
- enzyme regulation
- neurite outgrowth
- neurotransmission
- secretion
- control of gene transcription

Voltage-gated Ca^{2+} channels differ from Na^{+} channels in selectivity, gating and drug sensitivity





binding site of central depressant and anxiolytic drugs

Each α1 subunit is the pore-forming subunit with accessory subunits: $\alpha_2\delta$, β, γ
α_2 and δ are both the product of the same gene which encode a single precursor protein, which is post-translationally proteolytically processed into two polypeptides.

Each α_1 subunit has 4 homologous repeats (I–IV), each comprising of 6 TM segments (α helixes) and a **pore-forming region between S5 and S6** where there is the **selectivity filter**.
Like other voltage-dependent channels, **gating is governed by the *S4 segments*** containing highly conserved positive charges.

Ca^{2+} channels

There are **six molecular subtypes** of voltage-dependent Ca^{2+} channels (L, N, Q, R, P, T) regulating various cellular processes in the CNS and periphery. Each is encoded by different gene variants and each has a:

- distinct voltage-sensitivity profile (activation/deactivation kinetics)
- physiological / regulatory function
- pharmacology

L, P/Q, N and R are HIGH VOLTAGE-ACTIVATED channels
T is a LOW VOLTAGE-ACTIVATED channel

Calcium channels

Properties of voltage-dependent Ca^{2+} channels

Channel Type	L	N	T	P	Q	R
Conductance (pS)	25	13-20	5-9	9-20	16	15
Activation Threshold	High	High	Low	High	High	High
Deactivation Rate	Fast	Fast	Slow	Fast	Fast	Fast
Inactivation Rate	Slow	Moderate	Fast	Very Slow	Moderate	Fast
Permeability	$Ba^{2+} > Ca^{2+}$	$Ba^{2+} > Ca^{2+}$	$Ba^{2+} = Ca^{2+}$	$Ba^{2+} > Ca^{2+}$	$Ba^{2+} > Ca^{2+}$	$Ba^{2+} > Ca^{2+}$

10 genes encoding Ca^{2+} channels have been identified

Type	Voltage	α_1 subunit (gene name)	Associated subunits	Most often found in
L-type calcium channel ("Long-Lasting" AKA "DHP Receptor")	HVA (high voltage activated)	$Ca_v1.1$ (*CACNA1S*) $Ca_v1.2$ (*CACNA1C*) $Ca_v1.3$ (*CACNA1D*) $Ca_v1.4$ (*CACNA1F*)	$\alpha_2\delta$, β, γ	Skeletal muscle, smooth muscle, bone(osteoblasts), ventricular myocytes (responsible for prolonged action potential in cardiac cell), dendrites and dendritic spines of cortical neurones
P-type calcium channel ("Purkinje") /Q-type calcium channel	HVA (high voltage activated)	$Ca_v2.1$ (*CACNA1A*)	$\alpha_2\delta$, β, possibly γ	Purkinje neurons in the cerebellum / Cerebellar granule cells
N-type calcium channel ("Neural"/"Non-L")	HVA (high voltage activated)	$Ca_v2.2$ (*CACNA1B*)	$\alpha_2\delta/\beta_1$, β_3, β_4, possibly γ	Throughout the brain and peripheral nervous system.
R-type calcium channel ("Residual")	intermediate voltage activated	$Ca_v2.3$ (*CACNA1E*)	$\alpha_2\delta$, β, possibly γ	Cerebellar granule cells, other neurons
T-type calcium channel ("Transient")	LVA (low voltage activated)	$Ca_v3.1$ (*CACNA1G*) $Ca_v3.2$ (*CACNA1H*) $Ca_v3.3$ (*CACNA1I*)		neurons, cells that have pacemaker activity, bone (osteocytes)

Ca^{2+} channel blockers mostly used in research experiments

L channel are mainly sensitive to DHP
N at ω-conotoxin GVIA
P at ω-agatoxinIVA
T at Ni^{2+} and mibefradil

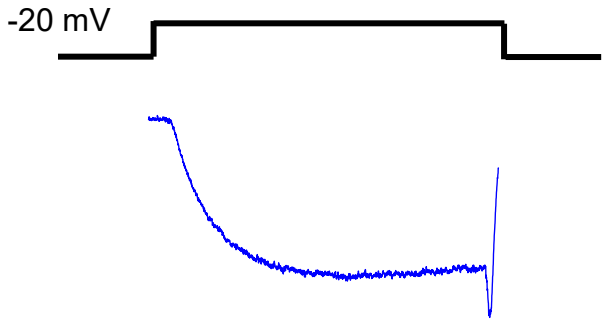
Selected calcium channel blockers for the treatment of neurological or psychiatric conditions

Compound (company)*	Targets	Main indications	Possible indications	Status‡	Refs
Isradipine (Dynacirc; Reliant)	L-type channels	Hypertension	Parkinson disease and dependency	Approved, Phase III trial for Parkinson disease	170,207
Nimodipine (Nimotop; Bayer)	L-type channels and T-type channels	Hypertension	Febrile seizures	Approved	154
Cilnidipine (Atelec/Cilacar; Fuji/Ajinomoto)	L-type channels and N-type channels	Hypertension	Pain and tremor	Approved	70,143
Gabapentin (Neurontin; Pfizer)	Cavα2δ subunits	Pain and epilepsy	Anxiety	Approved	148
Pregabalin (Lyrica; Pfizer)	Cavα2δ subunits	Pain and epilepsy	Anxiety	Approved	82,148,221
Lamotrigine (Lamictal; GlaxoSmithKline)	R-type channels (NS)	Epilepsy and bipolar disorder	Pain	Approved	149,150
Topiramate (Topamax; Mylan)	R-type channels (NS)	Epilepsy	Weight loss, addiction and PTSD	Approved	152,153
Zonisamide (Zonegran; Eisai)	T-type channels (NS)	Epilepsy	Pain and Parkinson disease	Approved	145
Ethosuximide (Zarontin; Pfizer)	T-type channels	Epilepsy	Pain	Approved	101,140
Ziconotide (Prialt; Elan)	N-type channels	Pain	NA	Approved	86–91
Valproate (Depakene/ Convulex; Abbott)	T-type channels (NS)	Epilepsy and bipolar mania	Parkinson disease	Approved	143,145
Z944 (Epirus)	T-type channels	Pain	Epilepsy	Phase II trial for pain	112,147
CNV2197944 (Convergence)	N-type channels	Pain	Anxiety and dependency	Phase II trial for pain	See the Convergence Pharmaceuticals press release
Z160 (Epirus)	N-type channels	Pain	Anxiety and dependency	Failed Phase II trial for pain	93

NA, not applicable; NS, not specified; PTSD, post-traumatic stress disorder. *The names of distributing pharmaceutical companies are shown in parentheses, although several of the compounds are now available as generic drugs. ‡Note that Z944 and CV2197944 are in clinical trials and not yet approved.

L-type Calcium channels

- **L-type Ca^{2+} channels**- originally described in cardiac muscle and peripheral neurones, are present in many excitable cells often in specific subcellular regions.
- *In skeletal muscle*, L-type channels are concentrated on T-tubule membranes and act as a voltage sensor for E-C coupling, linking membrane depolarization to Ca^{2+} release from intracellular stores.
- They are also important for *smooth muscle contraction*.
- *In neurones*, they are located primarily on cell bodies, and proximal dendrites, involved in the **processing of synaptic inputs at the somatodendritic level**. Entry of Ca^{2+} through L-type channels on the cell soma may also be involved in the regulation of enzymes and gene expression.



L-type Ca^{2+} channels

- **L-type Ca^{2+} channels**- open in response to *large* depolarizations (HVA), and do not inactivate significantly during depolarizations of hundreds of milliseconds (*L: long-lasting*), although some slow Ca^{2+}-dependent inactivation does occur.
- **L-type Ca^{2+} channel blockers include:**

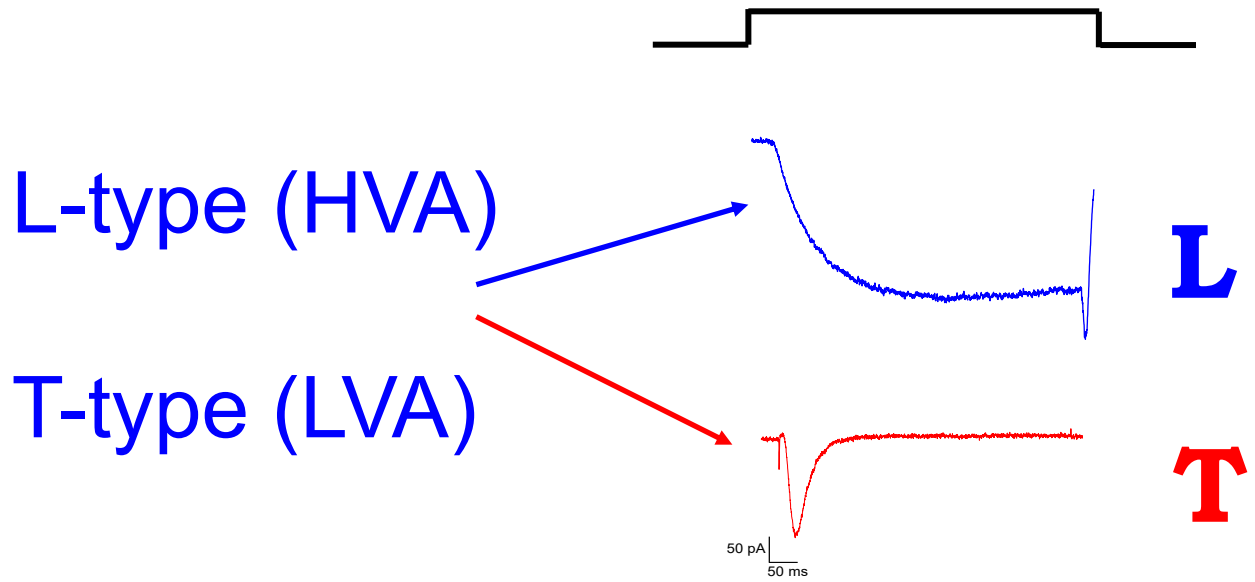
  DHPs- Nifedipine, Amilodipine, Nicardipine, Nimodipine **Verapamil**; Diltiazem
- **Toxins:** ω-Agatoxin IIIA (ω-Aga IIIA), isolated from the venom of the funnel web spider *Agelenopsis aperta*

N-type and P/Q-type calcium channels are **high-voltage-gated calcium channels contributing to vesicle release at synaptic terminals**.

Many neurological diseases with associated genetic factors such as migraine, multiple sclerosis, Huntington's have been related to a dysregulation of N-type channels.

A number of neurological diseases have been attributed to malfunctioning of P/Q channels, including ataxia, migraine and Alzheimer's disease.

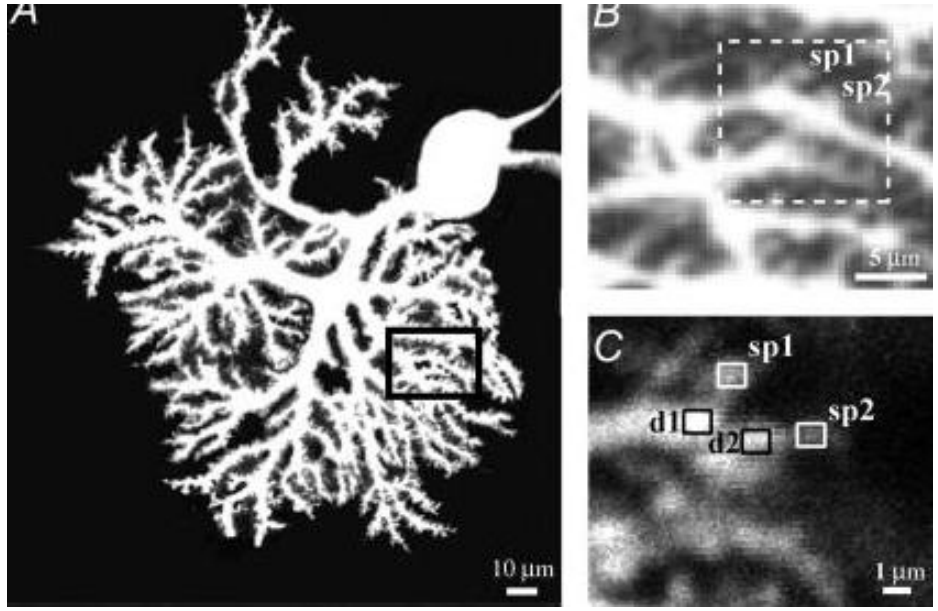
T-type Ca^{2+} channels are de-inactivated at hyperpolarized potentials and are activated by depolarization.
They partecipate in intrinsic oscillatory activity



L-type Ca^{2+} channels	*T-type Ca^{2+}channels*
• activation -30 mV • slow or no inactivation single channel conductance 25 pS • selectively blocked by dihydropyridines, phenylalkylamines benzothiazepines	• activation -65 / -50 mV • fast inactivation single channel conductance 8 pS • no selective blockers sometimes blocked by low [Ni^{2+}] or mibefradil

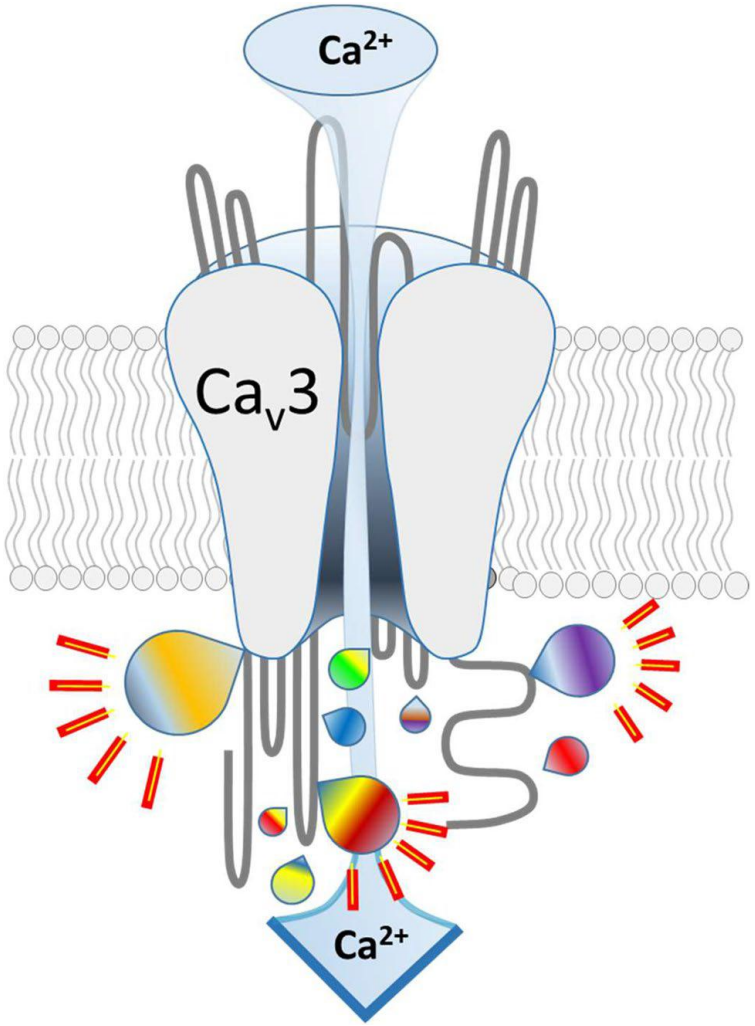
Detection of T-type Ca^{2+} channels

In many neurons T-type Ca^{2+} channels are predominantly expressed in the dendrites, often in distal portion



Isope & Murphy, 2005

In Purkinje cell dendritic Two-photon imaging revealed the expression of T-type Ca^{2+} channels at the level of single spines.
Compartimentalized Ca^{2+} signaling!



It will never work alone, multiprotein complex

T-type Ca^{2+} channel

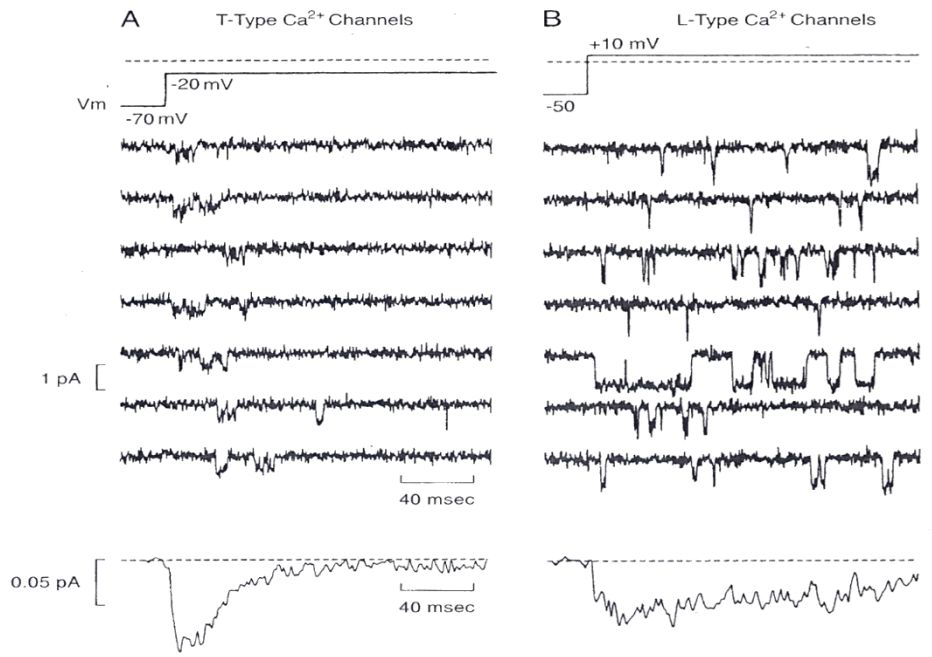
Eighteen such regulators are described, including syntaxin1A, β2γ2 G-protein, calmodulin, USP5, and STAC1.

Hence the “channelosome” theory

Developmental properties of voltage-gated Ca^{2+} channels

Early in development, there is a high amount of expression of T-type calcium channels.
During maturation of the nervous system, the expression of N or L-type currents becomes more prominent.

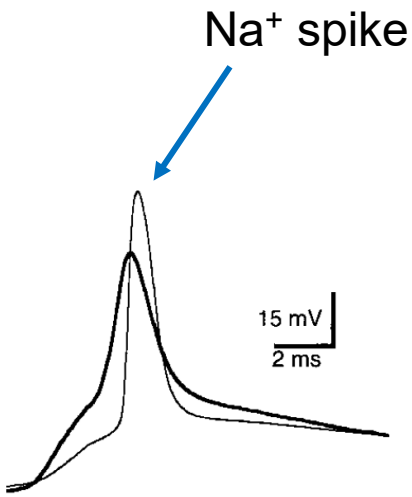
As a result, mature neurons express more calcium channels that will only be activated when the cell is significantly depolarized.



L-TYPE AND T-TYPE Ca^{2+} CURRENTS
Single-channel currents flowing through L-type and T-type Ca^{2+} channels recorded from a cell-attached patch on a guinea pig cardiac ventricular myocyte. Barium has been used as the permeant ion. Each of the seven upper current traces was elicited by a single depolarization, whereas the bottom trace respresents the average of ~280 such traces. (From Nilius et al. (1985).

Ion channels and disease, Academic Press

Neurons frequently fire on rebound from inhibition



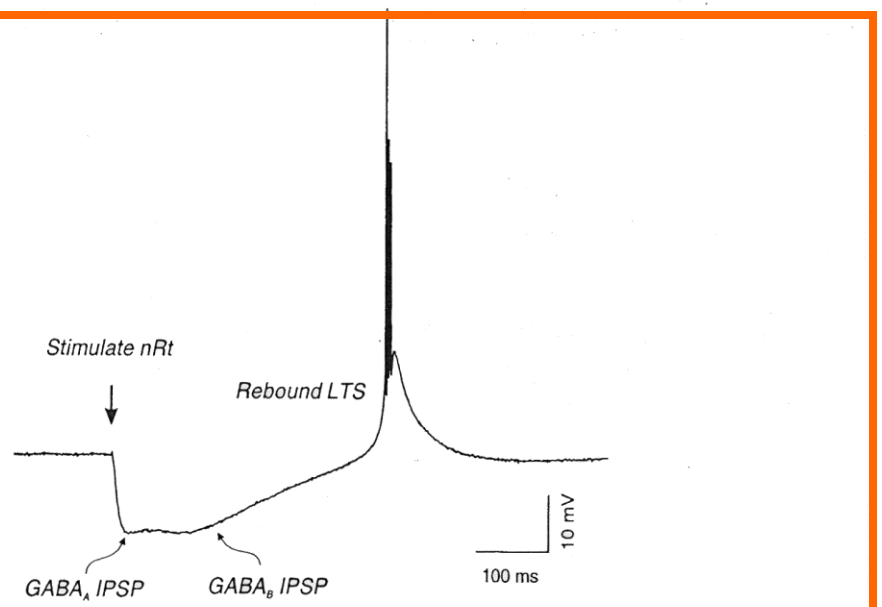
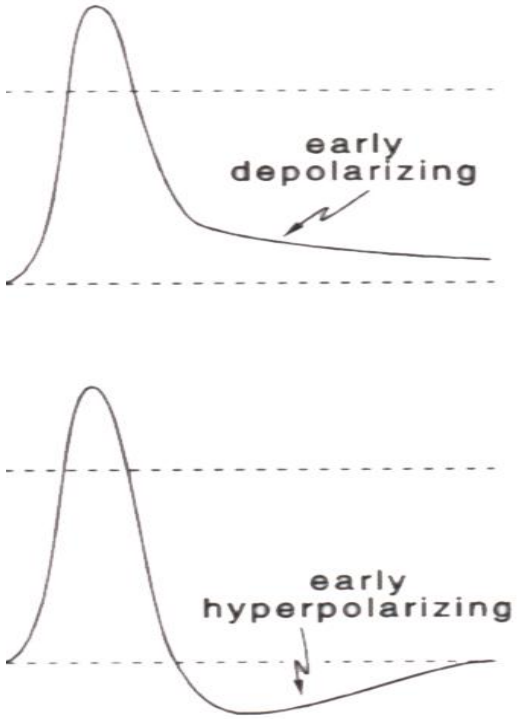


FIGURE 11-4. Activation of nRt results in strong inhibitory synaptic responses in relay neurons. Intracellular whole-cell recording in VB. nRt was activated through extracellular stimulation with a bipolar tungsten-stimulating electrode (250 μA 50 μsec), which resulted in a long-lasting hyperpolarization with an early Cl-dependent, bicuculline-sensitive $GABA_A$ component and a late K^+-dependent, CGP-35348 sensitive $GABA_B$ component. The inhibitory potential was of long enough duration to deinactivate I_T channels such that a rebound low-threshold spike (LTS) was obtained. Since VB output projects back to nRt, this circuit then is the basis for an intrathalamic oscillatory network.

Current-clamp mode

Time at which neurons fire will be partially determined by the time course and strength of that inhibition

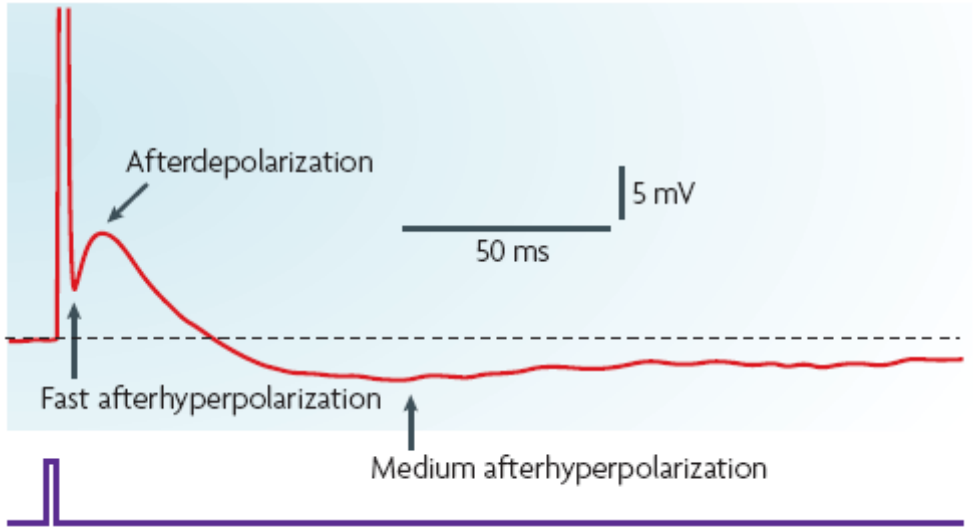
Post-spike hyperpolarization & depolarization

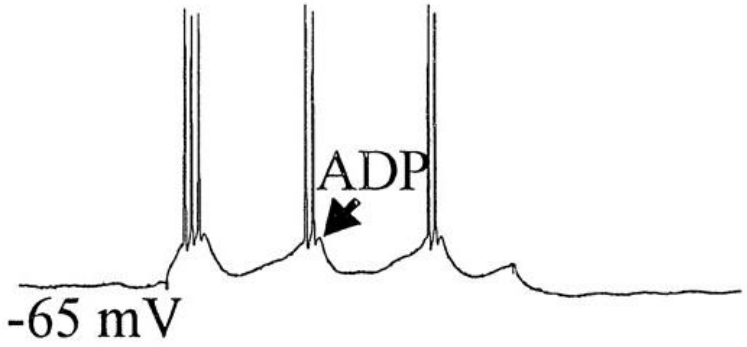


Cell Physiology, Academic Press

Ionic conductances contributing to ADP include:

I_{NaP} , I_T I_R I_{CAN}

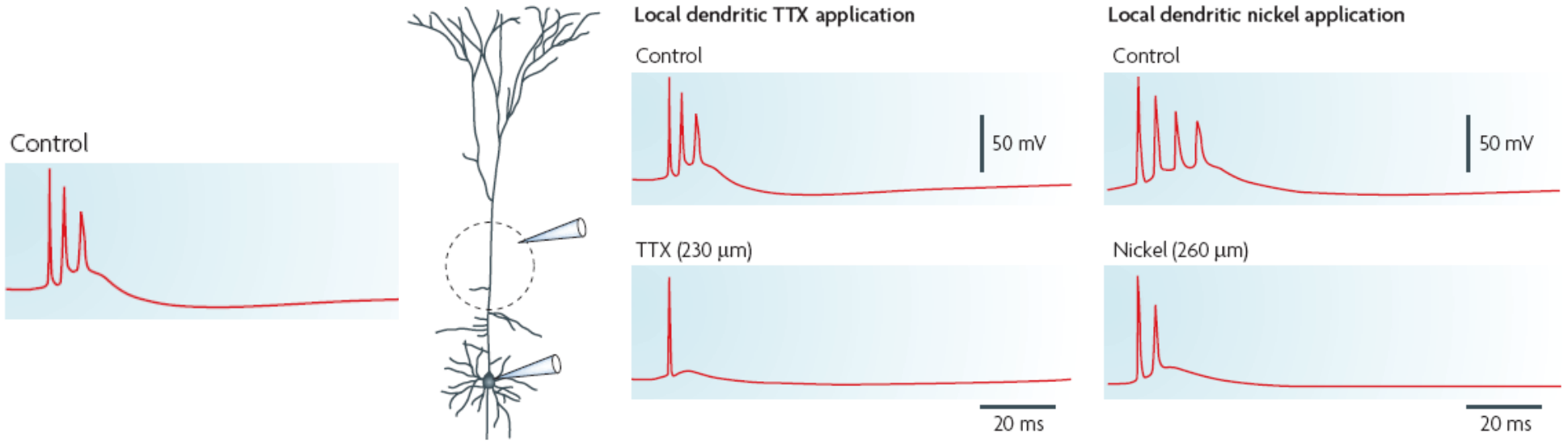




Sometimes the ADP follows burst discharges. In thalamic neurons T-type Ca^{2+} currents may be coupled to Ca^{2+}-dependent cationic currents leading to ADP following burst discharges.

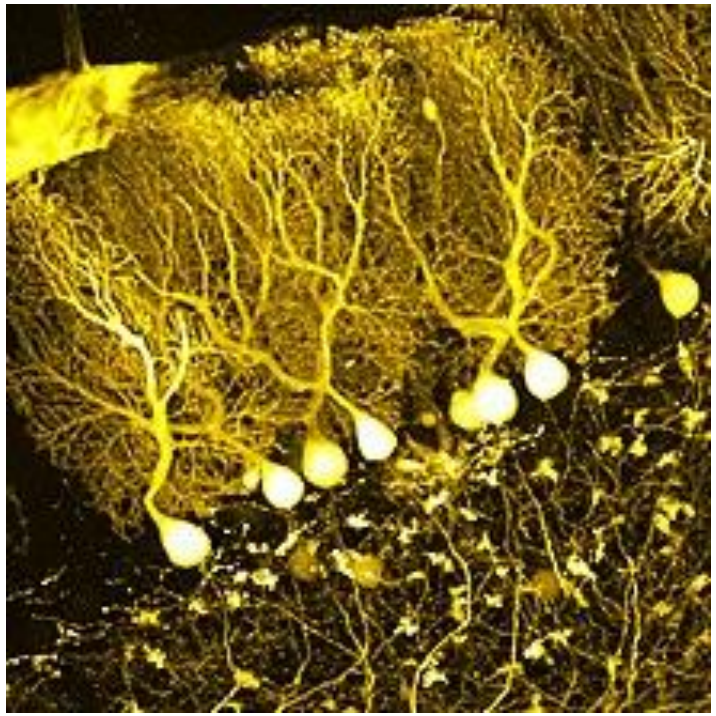
A backpropagation of AP induces a bursting activity

After the origin of AP at the trigger zone, the depolarization can pass back to the dendritic membrane and amplified by dendritic I_{Ca} and I_{Na} activated slowly inducing burst firing



The contribution of dendritic Na^+ and Ca^{2+} currents to burst firing in cortical PYR neurons

Failure of action potential invasion in multi-branched dendritic trees !!!



In any case, contemplating the form of the cells was one of my most beloved pleasures. Because even from an aesthetic point of view the nervous tissue has fascinating beauty. Are there in our parks any more elegant and lush trees than the Purkinje neuron in the cerebellum or the so-called psychic cell, that is, the famous cortical pyramidal neuron? (Ramón y Cajal 1923)

CaV1 (L-type) and CaV2 (N-, P/Q- and R-type) channels engage distinct modes of Ca^{2+} signaling
coupling membrane depolarization to signaling machinary

Cav1 exerts a dominant role in controlling gene expression signaling to the nucleus through CaMKII. It signals through Ca^{2+} acting on local signaling machinery.

ER and mitochondria selectively buffer Ca^{2+} entering through Cav2

N and P/Q-type channels mediate fast evoked neurotransmitter release

Wheeler et al., Cell, 2012