Theoretical & computational Neuroscience:

Programming the Brain

(BM 6140)

2-credit

Quantitative analysis of AP : Hodgkin-Huxley

- Hodgin, Huxley 1952, series of papers
- Nobel prize (1963) in physiology or medicine

Hodgkin-Huxley equations

After fitting curves, HH obtained

$$I_{inj} = C_m.\frac{dV}{dt} + I_{ion}(V,t)$$

$$I_{ion}(V,t) = I_{Na}(V,t) + I_K(V,t) + g_L.(V - E_L)$$

$$I_{Na}(V,t) = m^3(V,t).h(V,t).\overline{g}_{Na}.(V - E_{Na})$$

$$I_K(V,t) = n^4(V,t).\overline{g}_K.(V - E_K)$$

$$\frac{dm}{dt} = \frac{m_\infty(V) - m}{\tau_m(V)}$$
$$\frac{dn}{dt} = \frac{n_\infty(V) - n}{\tau_n(V)}$$
$$\frac{dh}{dt} = \frac{h_\infty(V) - h}{\tau_h(V)}$$

$$where\ x_\infty = \frac{\alpha_x}{\alpha_x + \beta_x}\ and\ \tau_x = \frac{1}{\alpha_x + \beta_x}$$

Note that $h_\infty < h_0, n_\infty > n_0$ and $m > m_0$

Qualitatively explain production of Action potential from x_∞ and τ_x graphs ?

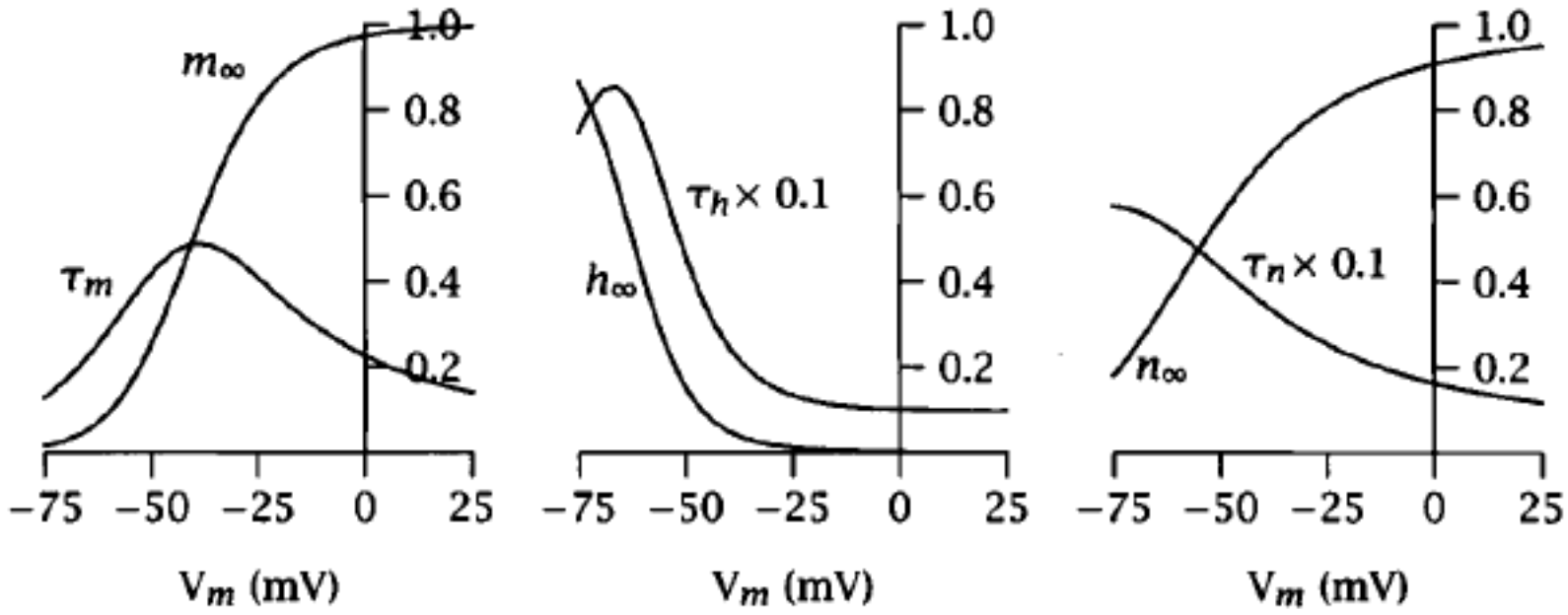


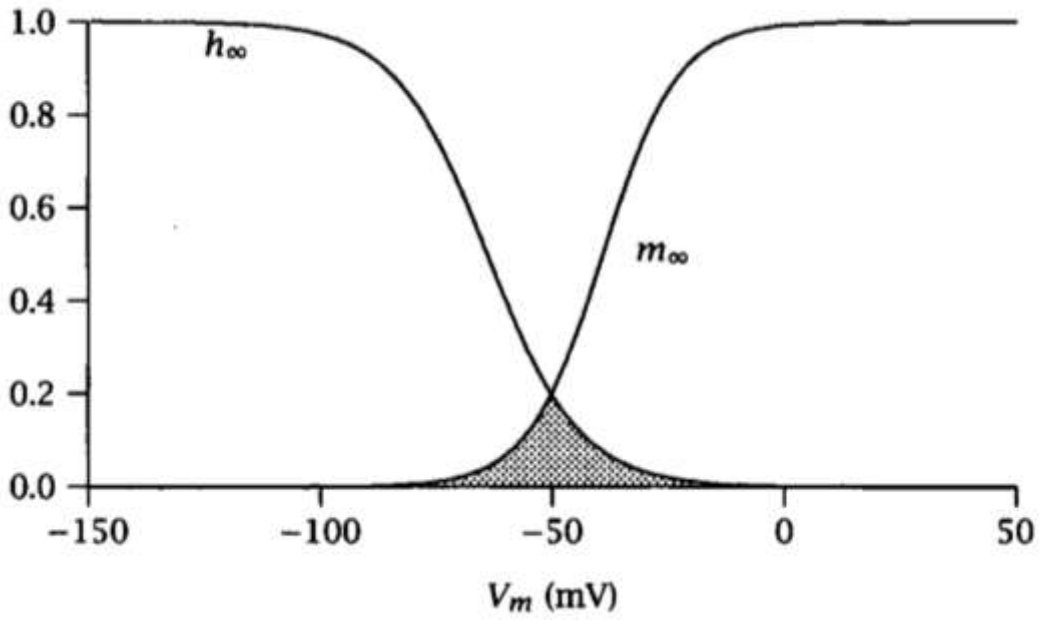
Figure 6.12 Steady-state activation curves (n_∞, m_∞, and h_∞) and the voltage dependence of the time constants of the Hodgkin and Huxley model.

Emergence of the AP (Qualitative)

- At voltages close to rest, K open, Na closed
- As voltages become more depolarized, Na opens a bit
- → More Na comes in to the cell
- → Cell becomes more depolarized
- Positive feedback pushes voltage to highly depolarized levels
- → Na channels shut down, K channels fully open and push out K fast ;
- → return to rest

Understanding the diversity in channel behaviour

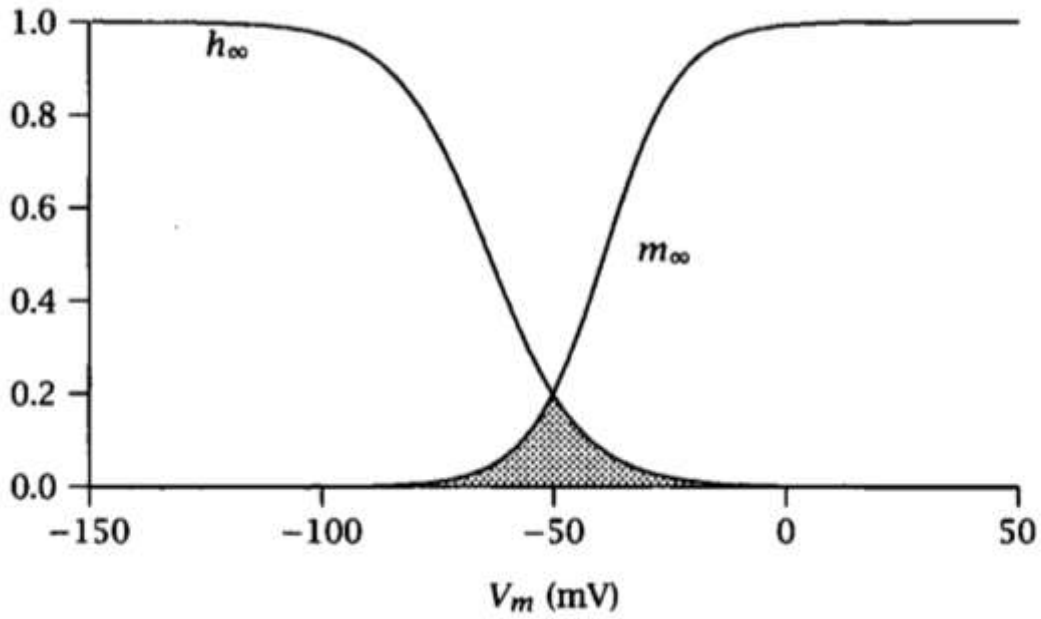
Say m_∞ and n_∞ are moved closer. When is I_{Na} max ? Compare with previous



Window current

At some voltage ranges h_∞ doesn't shut down fully while m_∞ is reasonably open such that their product is non negligible

How would the voltage clamp response look like ?



$I_{Na-Slow}$:
Non inactivating / slowly inactivating Na currents

- I_{Na} does not inactivate fully at ~-50 mV

- It does inactivate fully at more depolarized voltages

- Window current is just one mechanism to get non inactivating behavior.. Does not explain everything about $I_{Na-slow}$

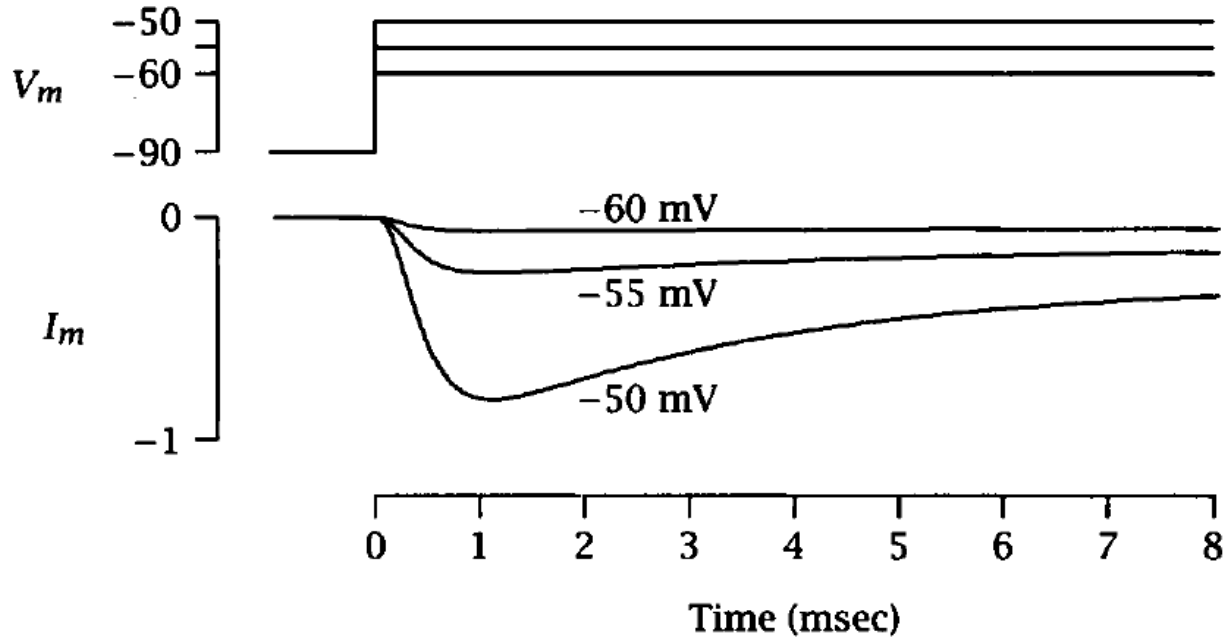
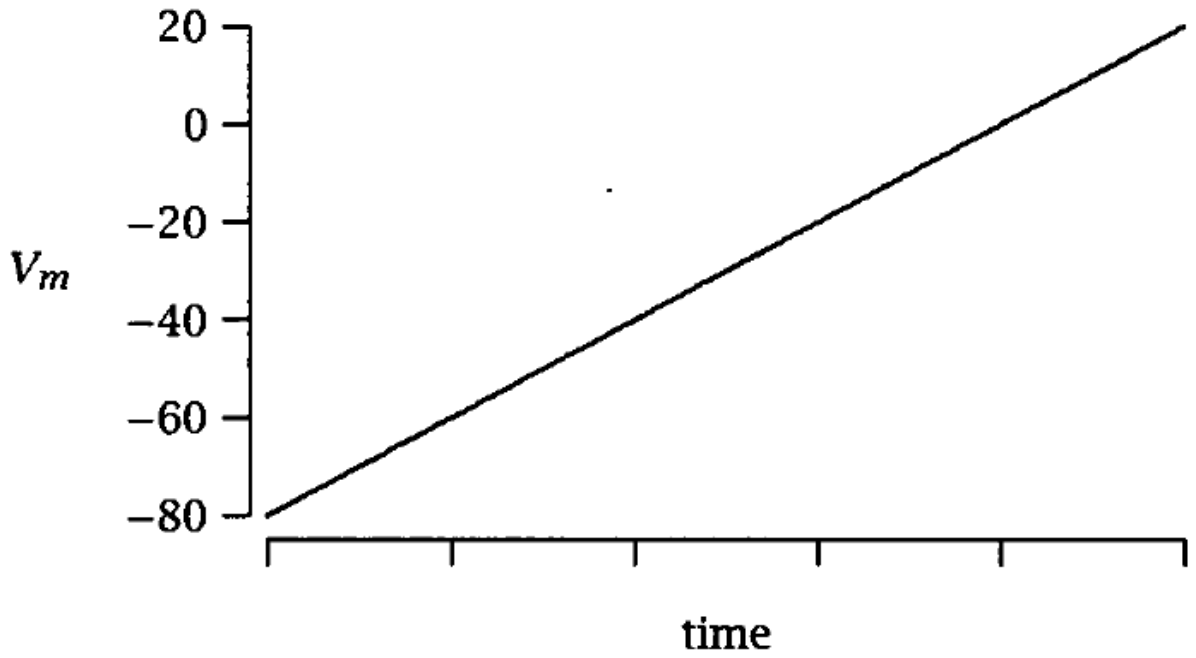


Figure 7.5 Voltage-clamp measurements of $I_{Na(slow)}$. Note that there is very little inactivation at −55 and −60 mV. V_m is in mV, and I_m is in nA.

Digression

What happens when instead of a voltage clamp you use a voltage ramp ?

Assume only a Sodium channel exists



Hint

You get the complete I-V curve in a single experiment !!

Provided, the slope is right w.r.t to the τ values

Separation of currents

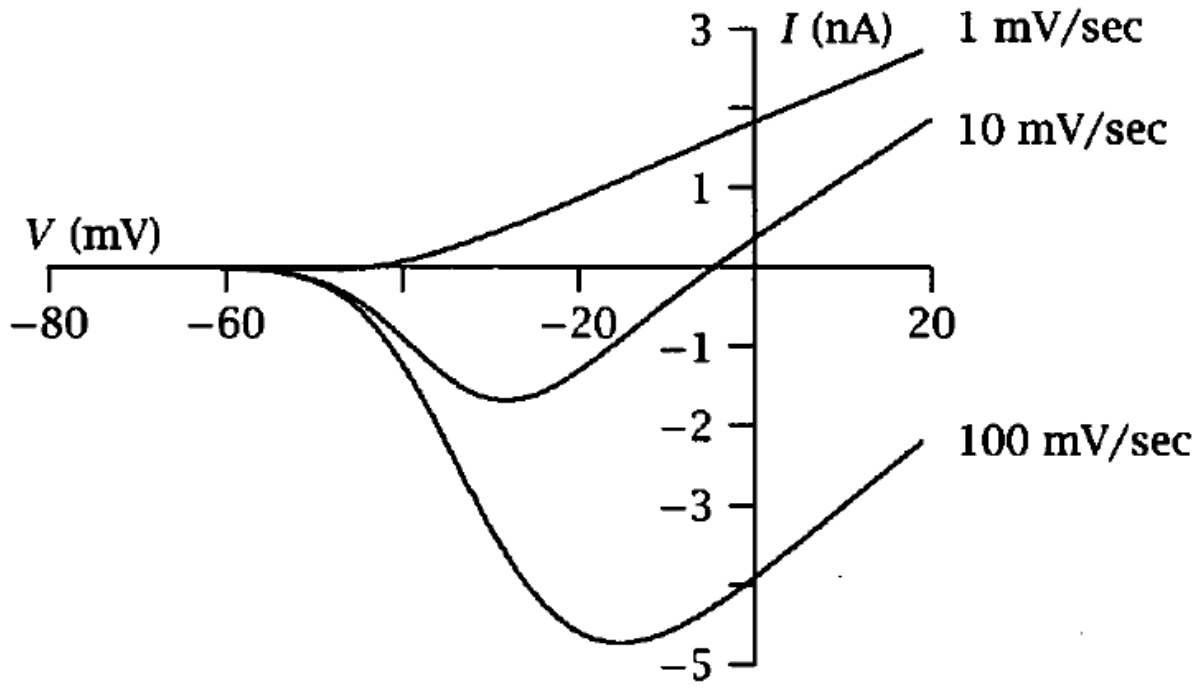
Assume you have 3 channels, K, Na(fast), Na(slow).

Give a voltage ramp with different slopes

What do you expect to see @

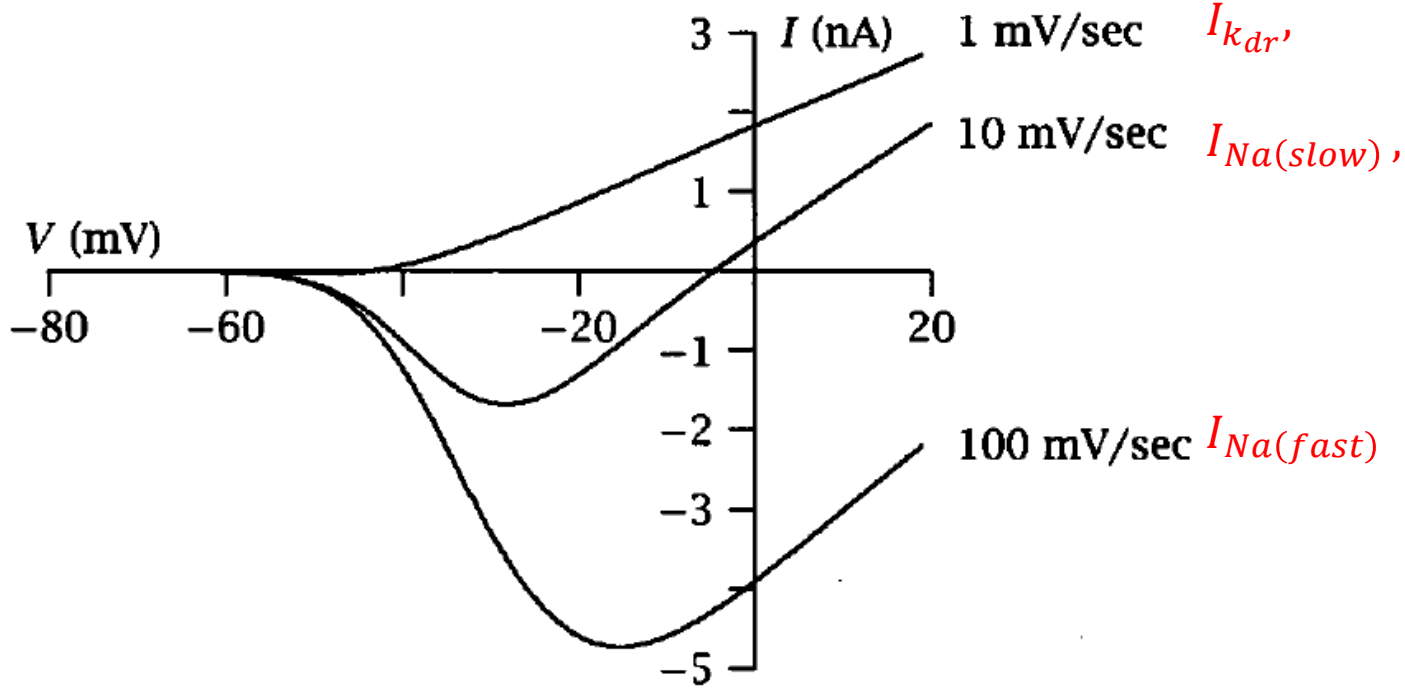
- very slow ramps ?
- very fast ramps ?
- intermediate slopes ?

Separation of slow and fast currents



Which of these curves belong to $I_{k_{dr}}, I_{Na(slow)}, I_{Na(fast)}$?

Separation of slow and fast currents



Effect of $I_{Na(slow)}$ on EPSPs / AP ?

Effect of $I_{Na(slow)}$ on EPSPs / AP ?

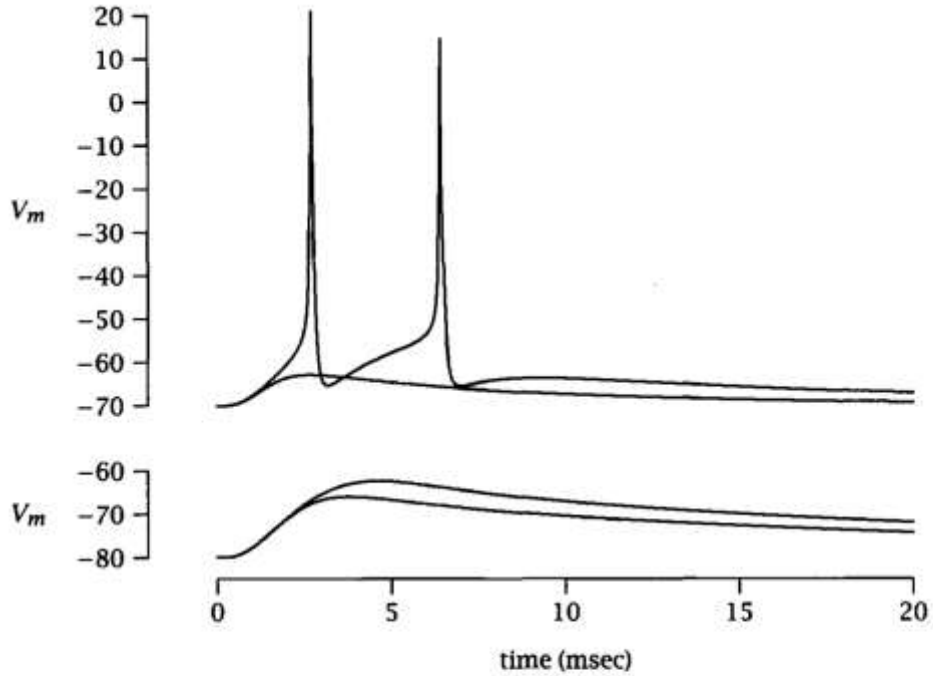


Figure 7.7 Amplification of EPSPs by $I_{Na(slow)}$. EPSPs are shown with and without $I_{Na(slow)}$ present in the neuron. The bottom set of traces are with the neuron hyperpolarized from rest. With $I_{Na(slow)}$ present the EPSP appears larger. At the normal resting potential (upper traces) the presence of $I_{Na(slow)}$ allows the EPSP to trigger APs. V_m is in mV.

Function of slow Na current ?

Hint

Which voltage range is it active ?

Now, retrace an Action potential and see where it would make a difference

Active near rest

→ Amplifies small deviations from rest

→ higher chances of firing an AP

K^+ channel diversity & Classification

By gating factors

- Voltage gated
- Ca^{2+} and voltage gated
- Hyperpolarisation gated
- Others

By function

- Contributing to Resting state
- Sub threshold activated
- Repetitive firing and afterpotential currents

K_{DR} - Delayed rectifier

- Similar to K^+channel in HH
- In hippocampal pyramidal neurons, very slow activation (time to peak = 50-100 ms) and even slower inactivations reported
- Dentate granule cells show activation time constants ~ 5 ms
- Blocked by TEA
- $I_{K(DR)} = m^3 h \bar{g}_{K(DR)} (V_m - E_K)$

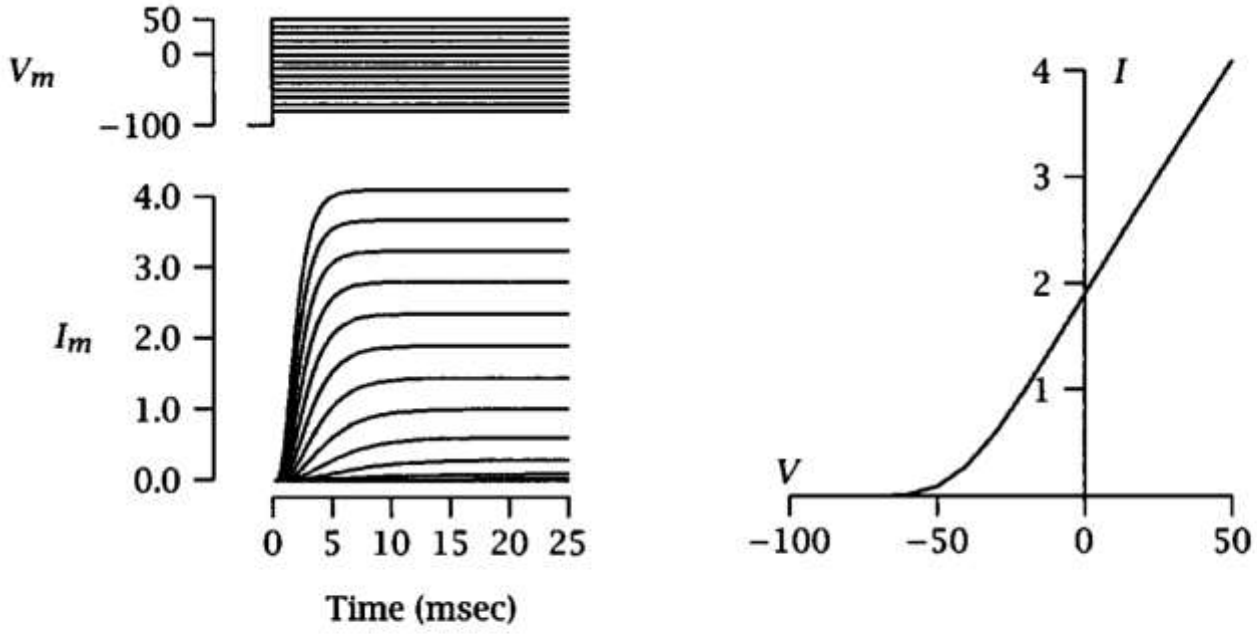


Figure 7.13 Activation of $I_{K(DR)}$ using step commands. A representative I-V curve is shown on the right. V_m is in mV, and I_m is in nA.

Q: What could be the function of K_{DR} ?

Q: Why is it called Delayed ? Rectifier ?

K_{DR} - Delayed rectifier

Repolarization post AP in Dentate granule cells but probably not in hippocampal pyramidal cells

Open only at depolarized potentials wrt rest and current flows only outwards..

Names are influenced by history and context too !

K_M - Non inactivating low threshold
Blocked by muscarinic receptor activation

Time course similar to K_{DR} but active at subthreshold voltages

Activation τ ~ 50 ms

Contributes to Spike train accomodation

K_A - transient, fast inactivating (4-**A**minopyridine sensitive current)

Active voltage range ?

Activation time ?

Inactivation time ?

What would it's function be ?

$$I_{K(A)} = mh\bar{g}_{K(A)}(V_m - E_K)$$

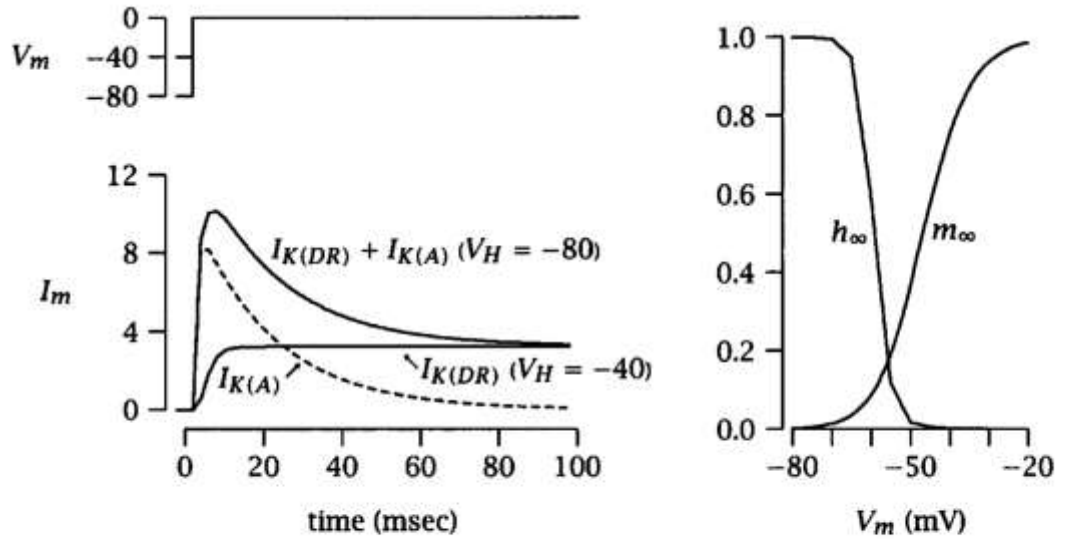


Figure 7.14 The properties of $I_{K(A)}$ and the separation of $I_{K(A)}$ from $I_{K(DR)}$ using different holding potentials are indicated. The activation and inactivation curves for $I_{K(A)}$ are shown on the right. V_m is in mV, and I_m is in nA. (Adapted from Connor and Stevens 1971b.)

K_A - transient, fast inactivating

Active voltage range ?

~ *-60 mV*

Activation time ?

~ 5-10 ms

Inactivation time ?

~ 20-30 ms

What would it's function be ?

- Spike repolarization

- Control bursting

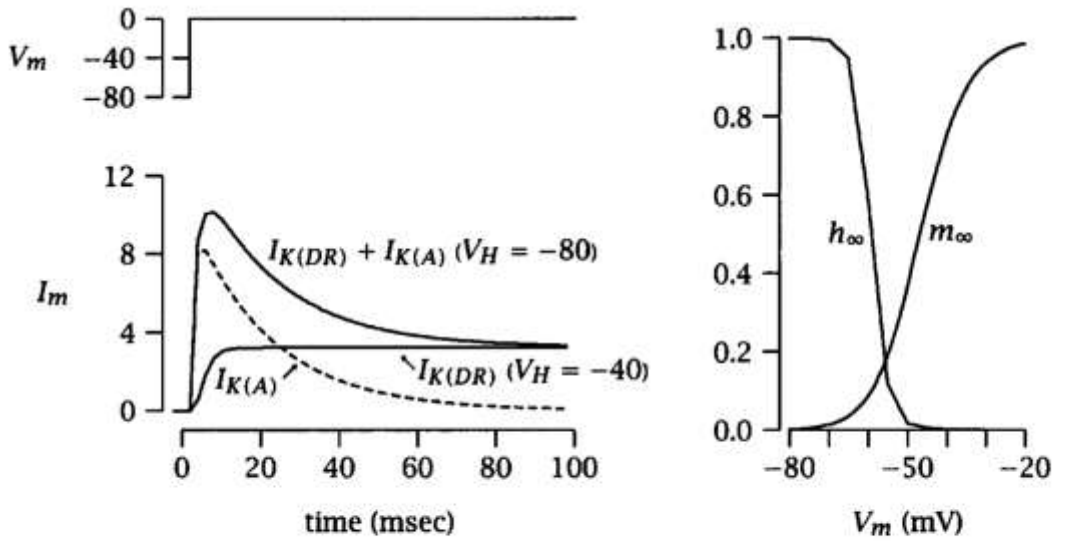


Figure 7.14 The properties of $I_{K(A)}$ and the separation of $I_{K(A)}$ from $I_{K(DR)}$ using different holding potentials are indicated. The activation and inactivation curves for $I_{K(A)}$ are shown on the right. V_m is in mV, and I_m is in nA. (Adapted from Connor and Stevens 1971b.)

K_D - Delay
Slow inactivating version of K_A

Active voltage range ?

H and m curves pushed left by 10-15 mV

Inactivation time ?

~ secs

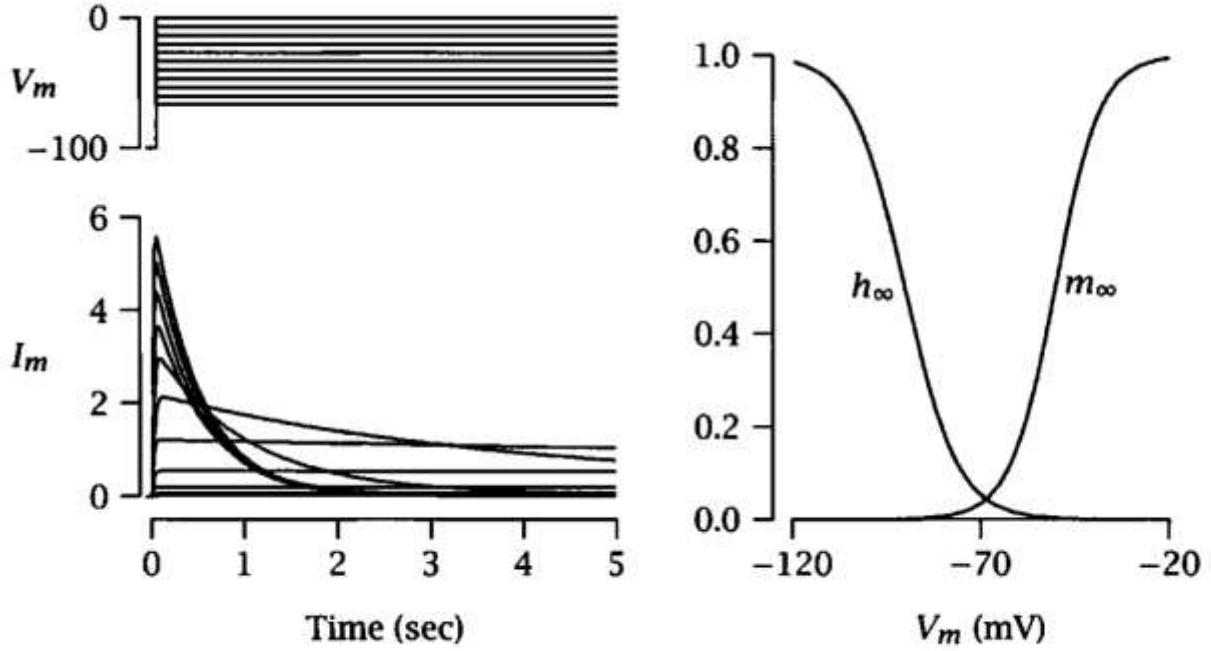
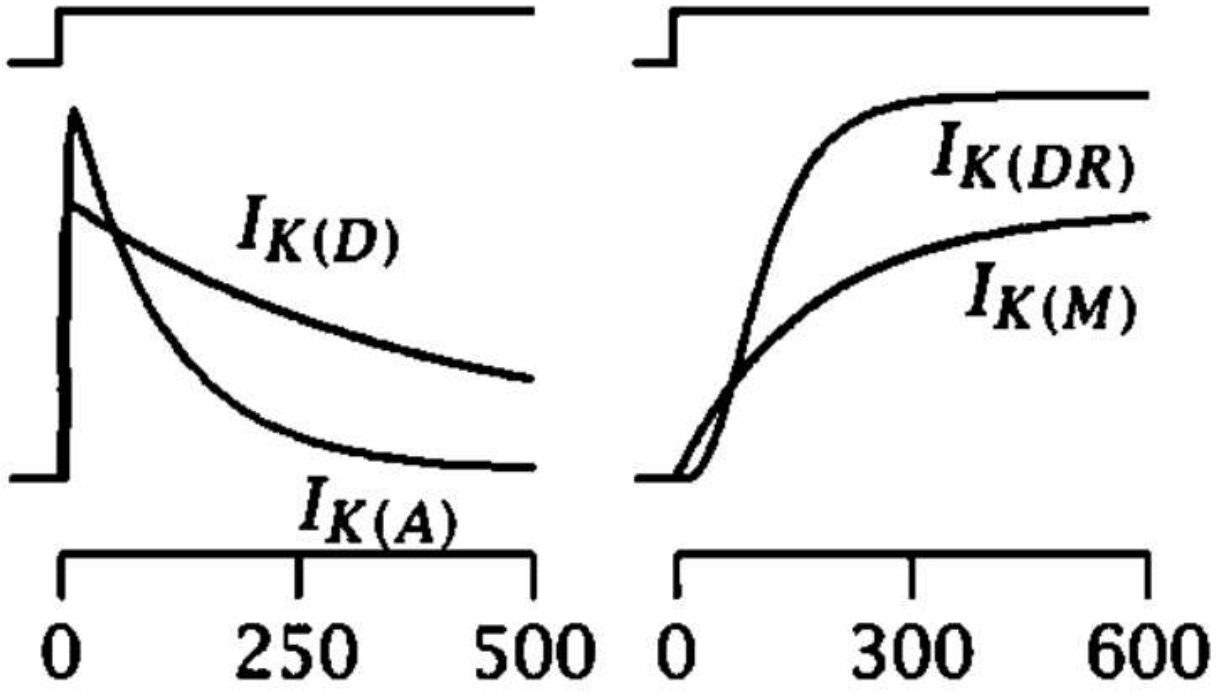


Figure 7.15 Properties of $I_{K(D)}$. Note the slower inactivation compared to that of $I_{K(A)}$. V_m is in mV, and I_m is in nA.

Interim summary
Depolarization activated K channels



K_C - Calcium+voltage gated

- Fast activation ~ 1-2 ms
- Inactivation ~ 100 ms
- Spike repolarization
- Repetitive firing

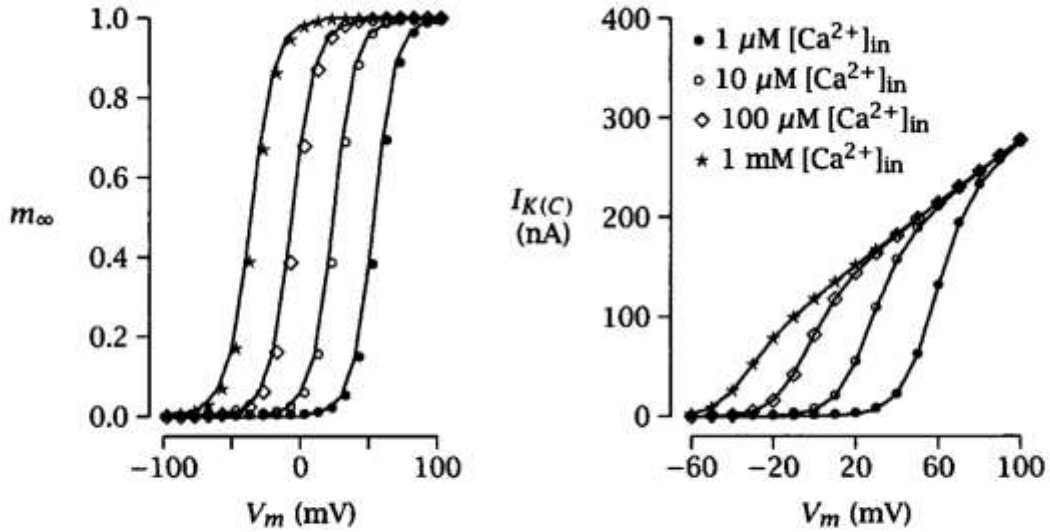


Figure 7.20 Voltage and Ca^{2+} dependence of $I_{K(C)}$. The activation curves at different internal Ca^{2+} concentrations are shown on the left with the resulting *I-V* curves indicated on the right.

$$I_{K(C)} = m_{(V+Ca)}\bar{g}_{K(C)}(V_m - E_K)$$

K_{AHP} - After HyperPolarization

- Smaller current than K_C
- Slower activation than K_C
- Function ??

$$I_{K(AHP)} = m_{Ca}\bar{g}_{K(AHP)}(V_m - E_K),$$

where m_{Ca} is dependent on $[Ca^{2+}]_{in}$ only

K_{AHP} - After HyperPolarization

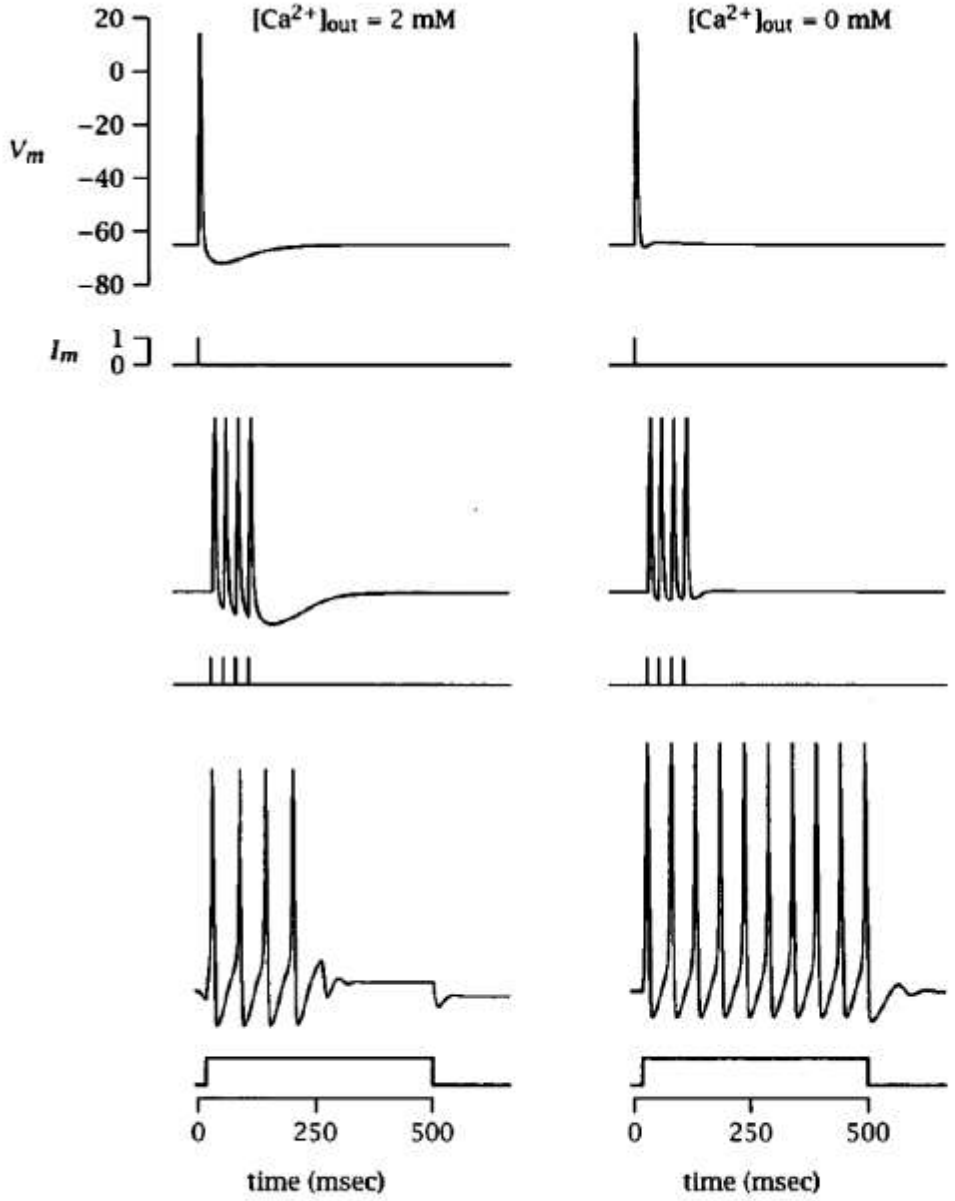
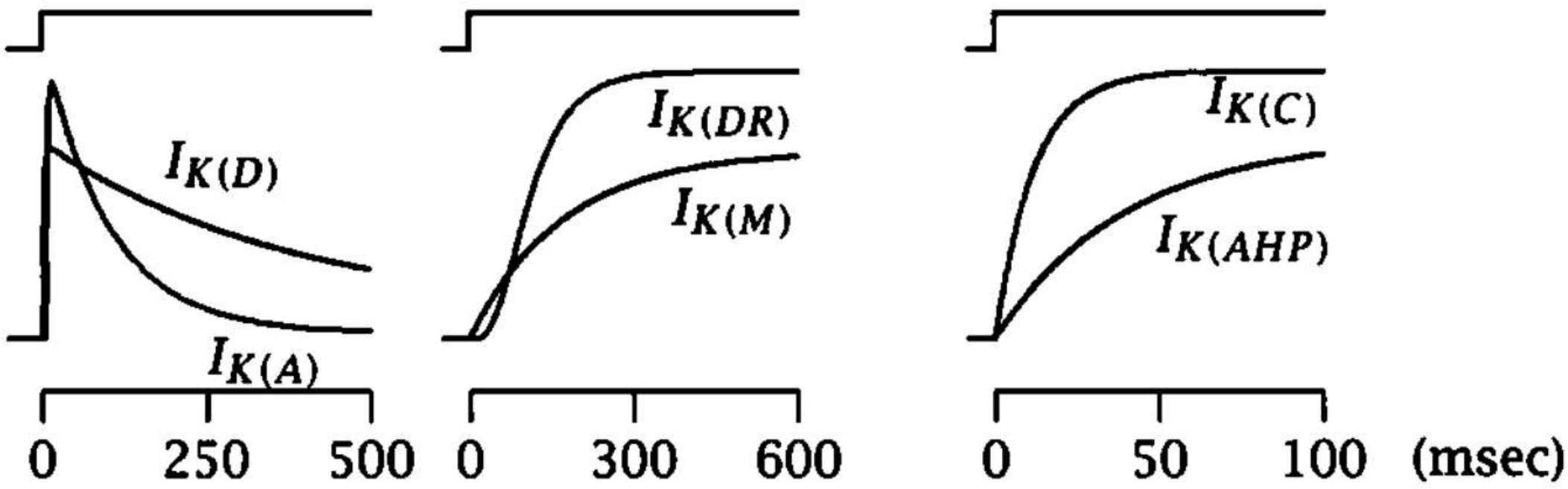


Figure 7.21 Properties of $I_{K(AHP)}$. $I_{K(AHP)}$ affects the firing frequency during a current step (I_m, bottom traces) and produces a slow hyperpolarization after a train of action potentials. $I_{K(AHP)}$ disappears in the absence of extracellular Ca^{2+}. V_m is in mV, and I_m is in nA.

Interim summary: K channels



Summary Functions of K^+ channels

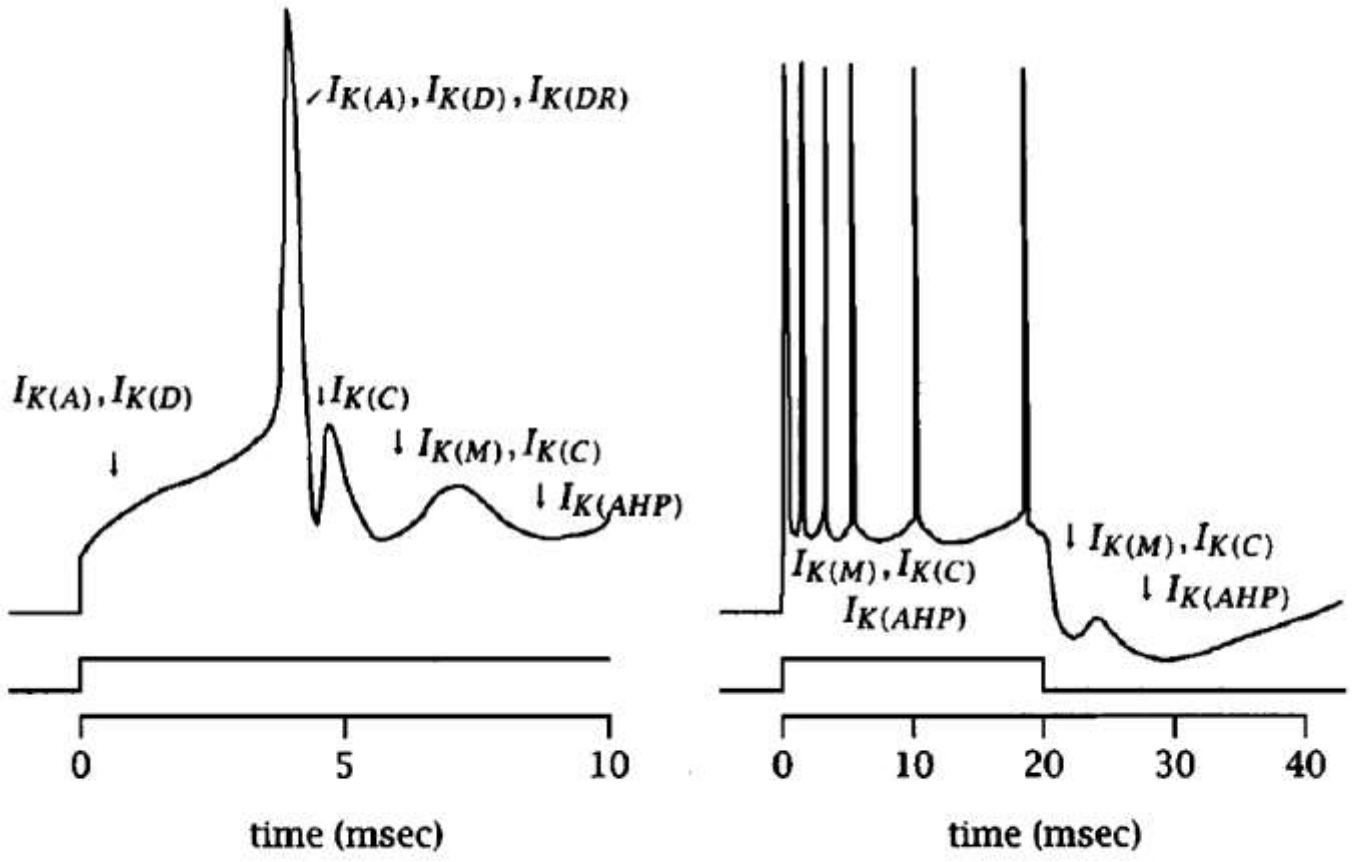


Figure 7.22 Effects of the various K^+ currents on different phases of an action potential in a cortical neuron. The current step is at the bottom. (Adapted from Storm 1990.)

K_{IR}- Inward rectifier Hyperpolarization activated

- Inward current elicited when hyperpolarized
- Behaviour depends on $[K^+]_{out}$
- Ion channel passes ions in inward direction better, hence inward rectifying
- Voltage dependence due to a Mg^{2+} block on the inside of the cell

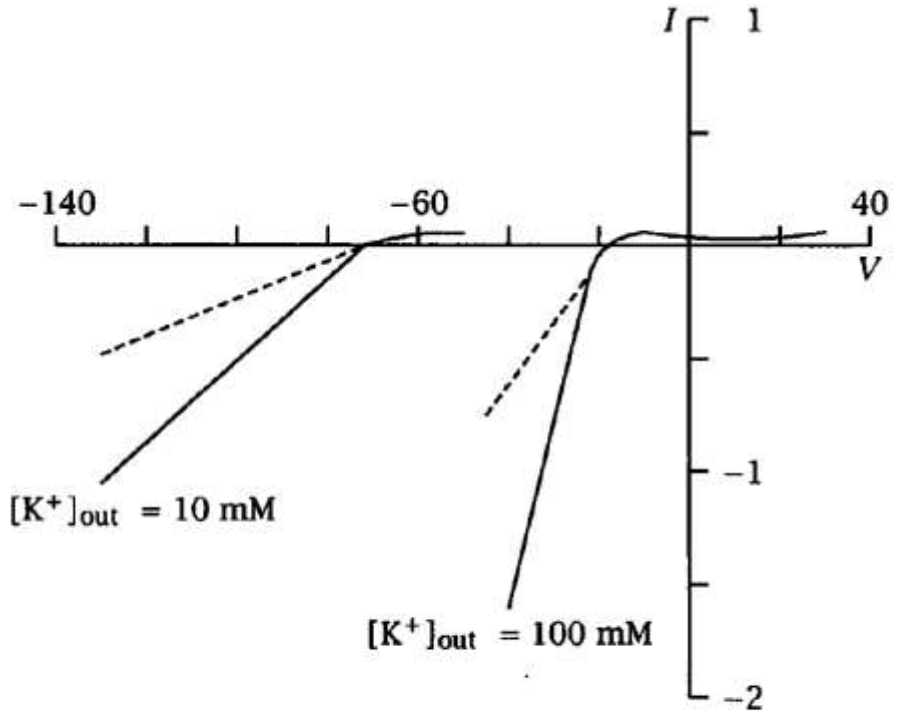


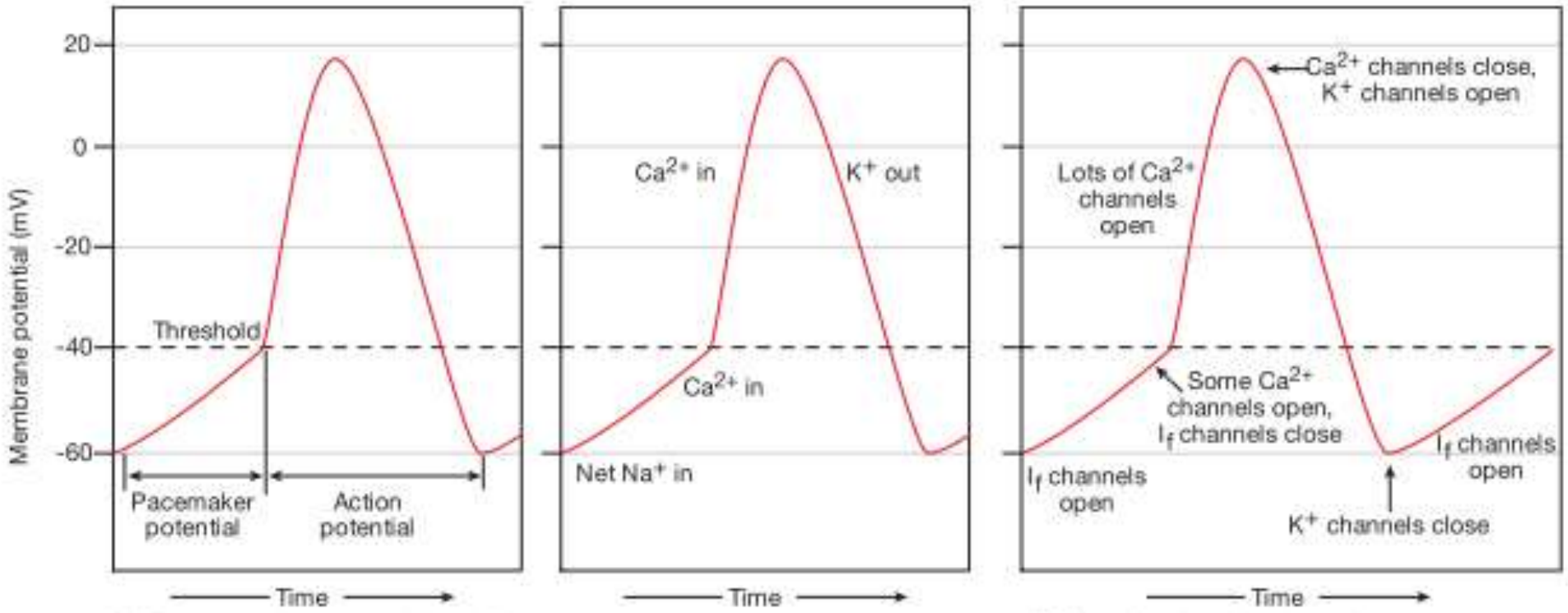
Figure 7.18 Properties of $I_{K(IR)}$ at different concentrations of extracellular K^+. The dashed line represents the membrane *I-V* curve in the absence of $I_{K(IR)}$. *V* is in mV, and *I* is in nA. (After Hagiwara et al. 1976.)

I_h, I_Q, I_f - {Hyperpolarization activated, Queer, Funny}
Non selective monovalent cation current

- Similar to K_{IR}
- Activated at voltages hyperpolarized wrt rest
- How would their current equation, ∞, τ curves look like ?

Cardiac Pacemaker cells

Presence of hyperpolarization activated cation non-specific channels and resultant Funny current (I_f) causes periodic firing



(a) The pacemaker potential gradually becomes less negative until it reaches threshold, triggering an action potential.

(b) Ion movements during an action and pacemaker potential

(c) State of various ion channels

Calcium currents

- Generally similar to Na^+currents, inward currents, has inactivating and non-inactivating varieties

- But Standard HH form for currents $I = m^x h^y . \overline{g}\ (V - E)$ not applicable to calcium currents

- Reason: Intracellular calcium levels are very low and there is practically no reversal potential E.

- Instead the GHK equation is used to calculate the ***steady state*** calcium currents as follows

$$I_{Ca_\infty}(V) = P_{Ca}\frac{4F^2}{RT}V\left(\frac{[\mathrm{Ca}^{2+}]_{in}e^{(2VF/RT)} - [\mathrm{Ca}^{2+}]_{out}}{e^{(2VF/RT)} - 1}\right),$$

where P_{Ca} is the Ca^{2+} permeability.

$Ca(L)$ - Long lasting, high threshold

- First known calcium current type
- Threshold voltages are depolarized wrt rest (Half max voltage ~ -15 mV)
- Activation depends on voltage
- Inactivation depends on intracellular calcium
- $I_{Ca(L)} = m_v^2 . h_{Ca} . I_{Ca(L)_\infty}(V)$

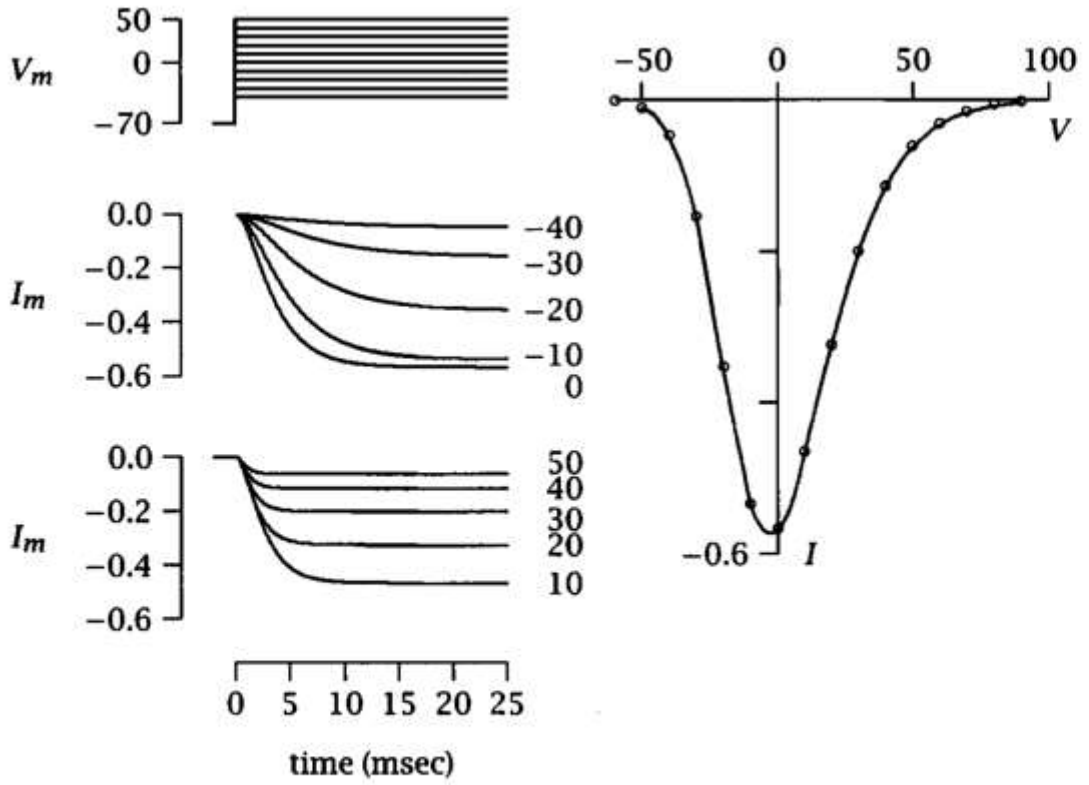


Figure 7.8 *I-V* curve (right) from whole-cell measurements of L-type Ca^{2+} currents (left). V_m is in mV, and I_m is in nA. The numbers to the right of each current trace are the command potentials (in mV) for that trace.

$Ca(T)$ - Transient, Low threshold

- Activated at potentials near rest ~ -40mV
- Voltage dependent inactivation, but not calcium dependant.. Hence transient
- $I_{Ca(T)} = m_v^2 . h_V . I_{Ca(T)_\infty}(V)$

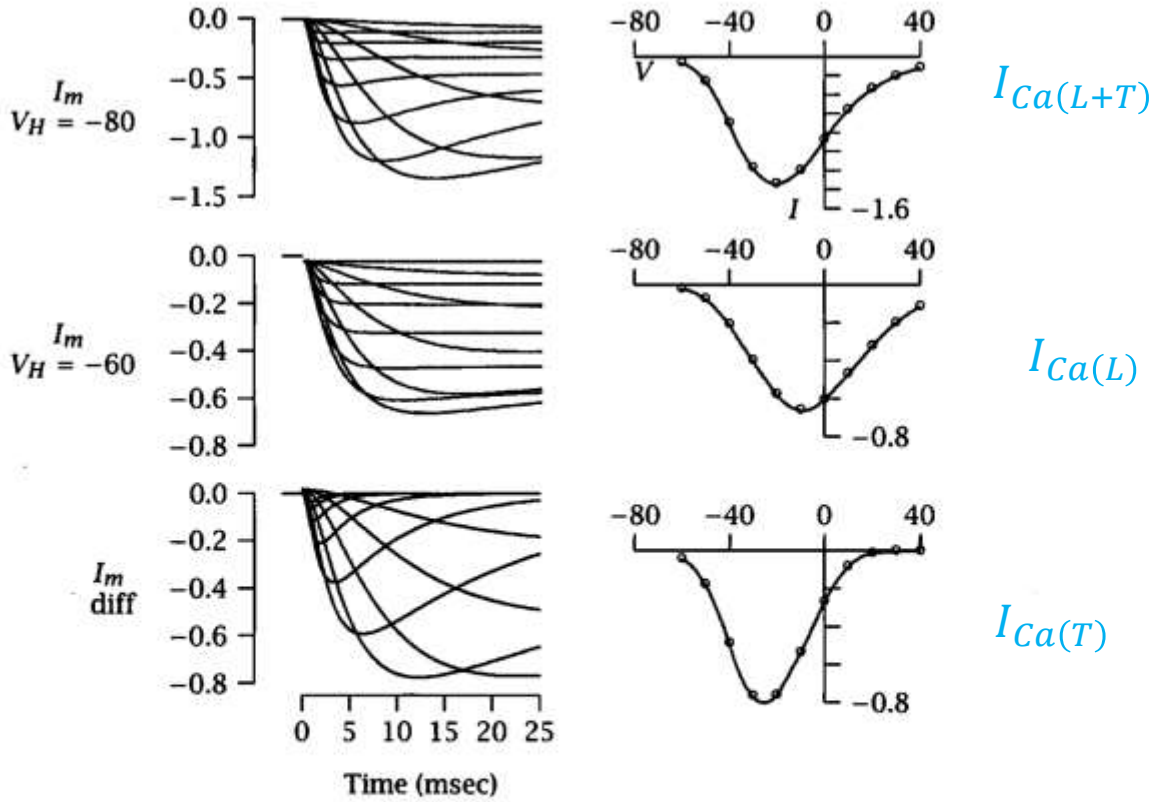


Figure 7.10 Separation of high- and low-threshold Ca^{2+} currents. Voltage steps from a negative holding potential (V_H = −80 mV) reveals an inward current that partly inactivates with time. The inactivating portion of this current (the low-threshold Ca^{2+} current) is obtained (lower left panel) by taking the difference between the currents measured from holding potentials of −80 mV and −60 mV. The *I-V* curves represent the measurements made at holding potentials of −80 mV (top right) and −60 mV (middle right), and the difference between the measurements made at −80 and −60 mV (bottom right). V_m is in mV, and I_m is in nA.

$Ca(N)$ - Neither T nor L, intermediate

- Activated at potentials between and L; half max ~ -25mV
- Voltage and Calcium dependent inactivation
- $I_{Ca(N)} = m_v^2 . h_V . h_{Ca} . I_{Ca(L)_\infty}(V)$

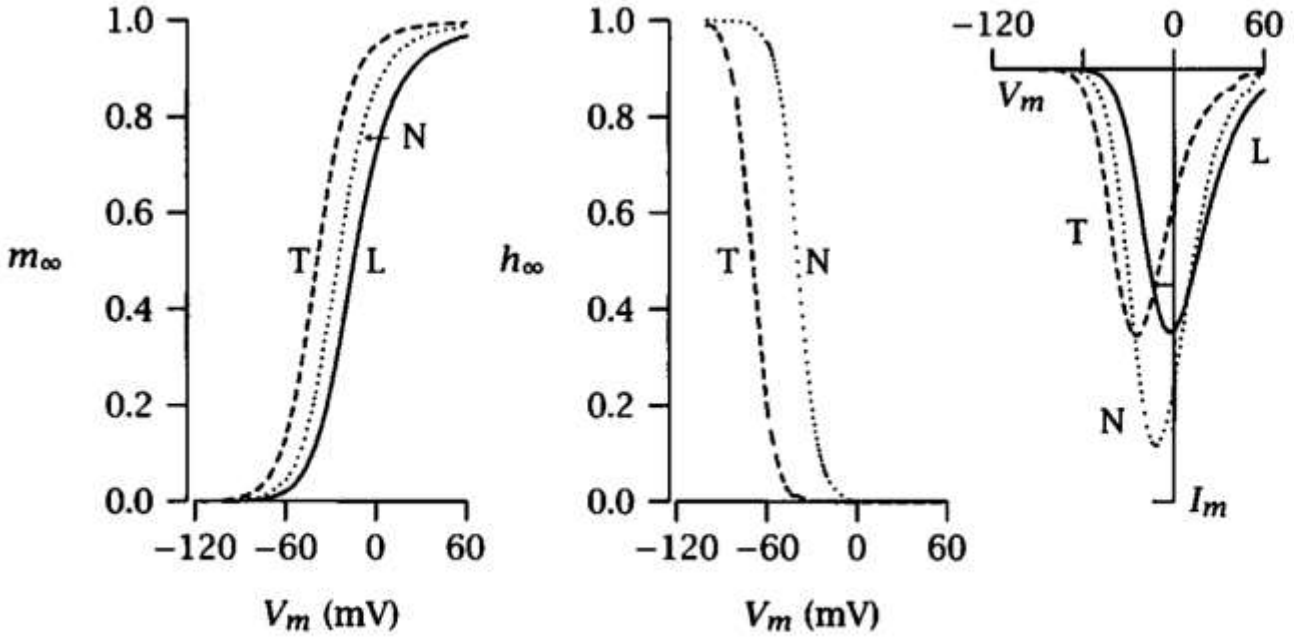


Figure 7.12 *I-V* curves and m_∞ and h_∞ for the L-, T-, and N-type Ca^{2+} currents. The P-type current has activation and inactivation properties similar to that of L.

Summary: Channel diversity

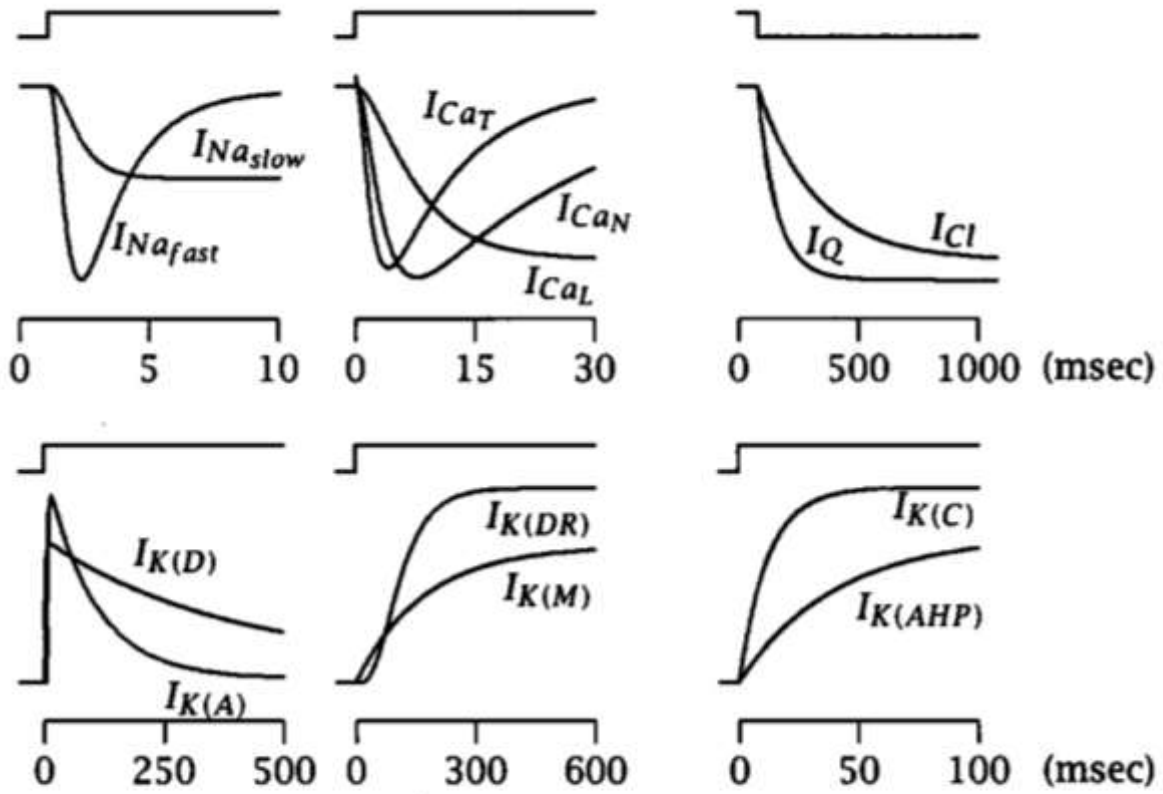


Figure 7.23 Comparison of the time courses of a number of different voltage and Ca^{2+}-dependent currents in hippocampal neurons. The voltage commands used to elicit each current are indicated at the top of each set of traces. (Adapted from Storm 1990.)

Ref

Table 7.1 Voltage-gated ionic currents in cortical neurons

Current	Symbol	Ion	V_{th}	Inactivation	Blocked by	Modulation	Function
1. Voltage-gated (depolarization)							
Na^+ currents							
Fast	$I_{Na(fast)}$	Na^+	−50	Fast	TTX		spike
Slow	$I_{Na(slow)}$	Na^+	−65	Slow	TTX		prepotential
Ca^{2+} currents							
High-threshold	$I_{Ca(L)}$	Ca^{2+}	−15	Slow Ca^{2+}-dep	Cd^{2+} DHP	NE (+) ACh (−)	spike
Low-threshold	$I_{Ca(T)}$	Ca^{2+}	−40	Fast V-dep	Ni^{2+}	ACh (+)	burst firing
High-threshold	$I_{Ca(N)}$	Ca^{2+}	−25	Medium V & Ca^{2+}-dep	Cd^{2+} ωCTX-GVIA	NE (+,−) Aden. (−) Others (−)	spike (?) presyn. (?)
High-threshold	$I_{Ca(P)}$	Ca^{2+}	−20	Slow	ωAga-IVA		presyn. (?)
K^+ currents							
Delayed rectifier	$I_{K(DR)}$	K^+	−40	Slow	TEA (10 mM)		
Transient	$I_{K(A)}$	K^+	−60	Fast	4-AP (> 0.1 mM)	ACh (−)	spike repolar.
Delay current	$I_{K(D)}$	K^+	−75	Slow	4-AP (< 0.1 mM)	DTX	delayed firing, spike repolar.
M current	$I_{K(M)}$	K^+	−65	None	Ba^{2+}	ACh (−) 5-HT (−) Somato. (+)	spike train accommod. *m*AHP

Ref

Current	Symbol	Ion	V_{th}	Inactivation	Blocked by	Modulation	Function
2. Voltage-gated (hyperpolarization)							
Slow inward rectifier	I_Q, I_h, I_f	Na + K	−60	None	Cs^+, THA		rest V_m
Fast inward rectifier	$I_{K(IR)}$	K^+	−80	Slow	Cs^+, Ba^{2+}	G_o (+)	
Time-depend. Cl^- currents	$I_{Cl(V)}$	Cl^-	−20	None	Cd^{2+}	PBs	dendrites (?)
		Cl^-	−60	None	Cd^{2+}		
3. Ca^{2+}-gated							
Fast K^+ current	$I_{K(C)}$	K^+	−40	None	TEA (1 mM)		spike repolar. *f&m*AHP
Slow K^+ current	$I_{K(AHP)}$	K^+	None	None	Ba^{2+}	ACh (−) NE (−) 5-HT (−) Hist. (−)	spike train accommod. *s*AHP
Cl^- current	$I_{Cl(Ca)}$	Cl^-					
Cation current		Na + K				ACh (+)	AHP (?)
4. Other currents							
Leak (?)	$I_{K(L)}$	K^+	None	None	Ba^{2+}	ACh (−)	rest V_m
Cl^-	I_{Cl}	Cl^-					
Anoxic	$I_{K(ATP)}$	K^+					hyperpol.
Na^+ Act. K^+	$I_{K(Na)}$	K^+					
Stretch		Na + K					mechanorec.