

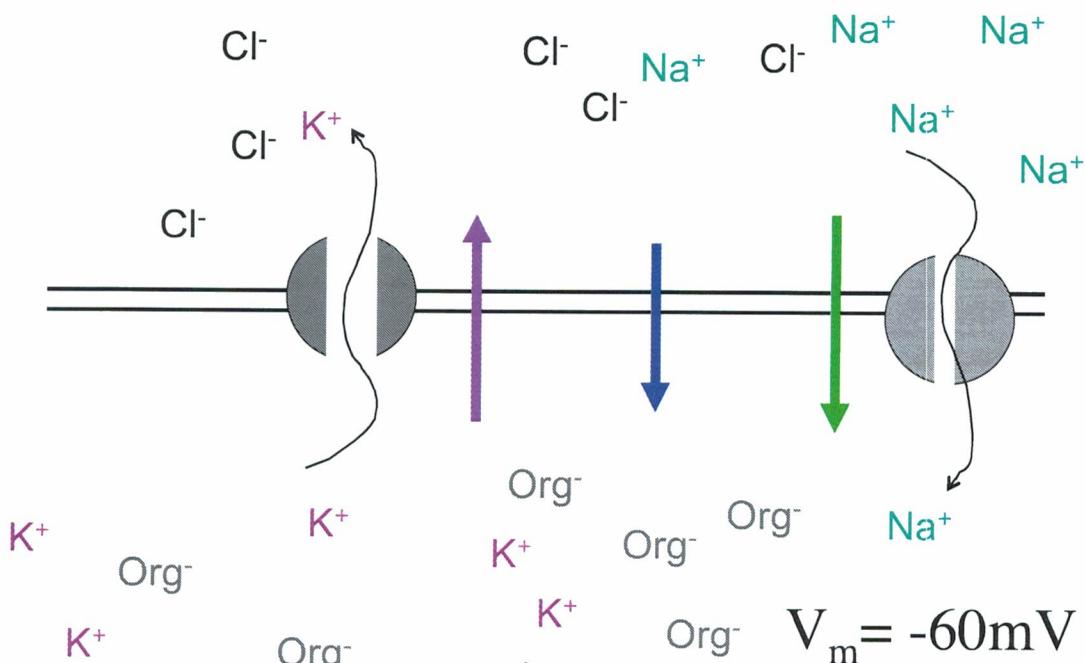
## Nernst/equilibrium Potential

- Nernst Potential for  $K^+$  ~ -75mV
- Nernst Potential for  $Na^+$  ~ +55mV
- Nernst Potential for  $Cl^-$  ~ -60mV
- REMEMBER: Nernst Potential for an ion depends upon the concentration gradient in the cell in question.

## Ionic currents produce changes in membrane potential

- Rate of ion movement depends upon driving forces acting on the ion
- Rate of ion movement also depends upon the permeability of the membrane to that ion
- Relative permeability of the membrane to potassium vs sodium is crucial in determining NET movement of charge

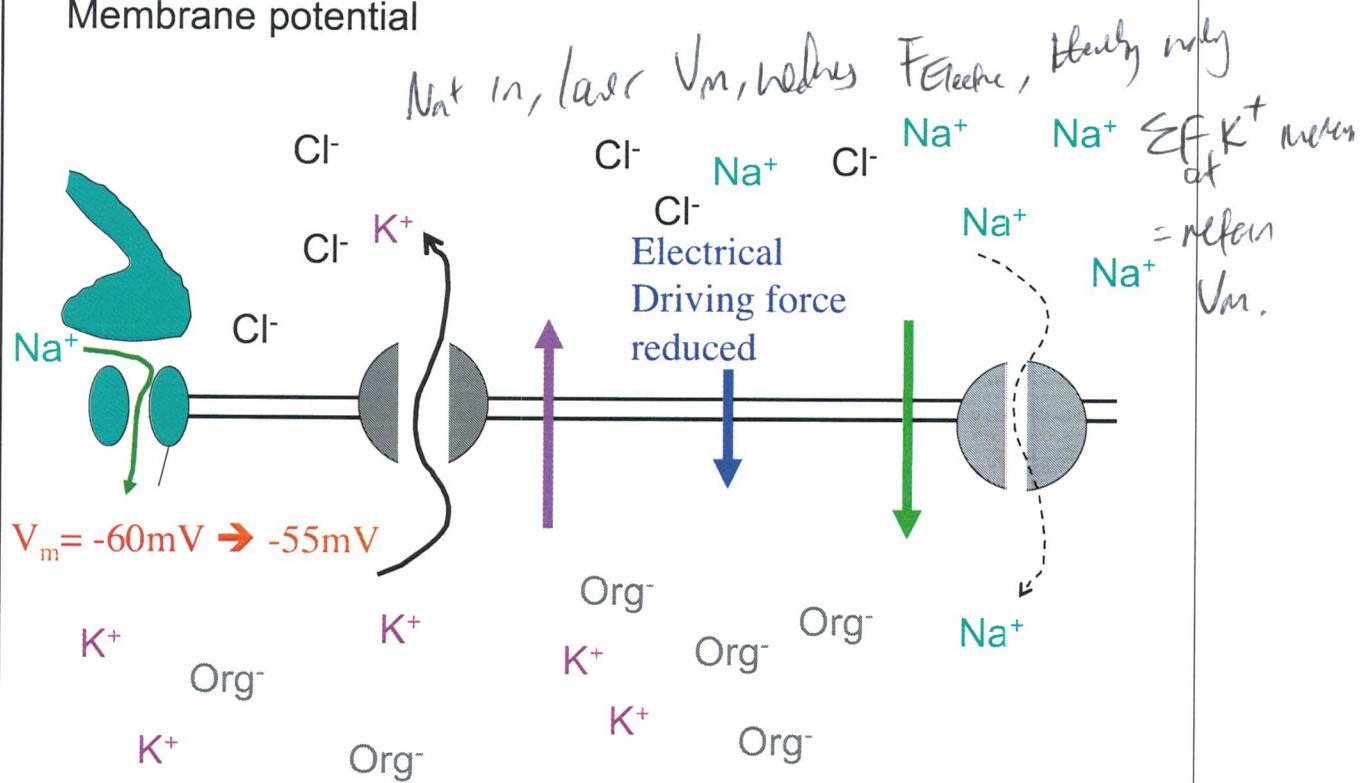
Electrical driving force on all cations ( $\text{Na}^+$  and  $\text{K}^+$ )  
 Chemical driving force on  $\text{Na}^+$   
 Chemical driving force on  $\text{K}^+$



would be 20x more permeable to  $\text{K}^+$  than  $\text{Na}^+$

leakage channels buffer membrane potential.

The leakage conductances of the cell help 'buffer' the resting Membrane potential



## Leakage currents “buffer” the resting membrane potential

- If  $V_m$  were to suddenly rise due to a synaptic input, the reduced electrical driving force automatically compensates by increasing the outward flow of potassium and reducing the inward leakage of sodium
- If  $V_m$  suddenly falls, the increased inward electrical driving force drives more sodium ions in through leakage channels to bring  $V_m$  back to its natural resting value.

## Net force on each ion:

- Is the sum of the chemical and electrical forces
- Chemical driving forces are very stable over time (don't change much)
- Electrical driving forces apply to all ions
- The Electrical driving force changes every time the membrane potential changes

## Relative permeability to ions

- When the membrane is permeable only to  $K^+$ , the membrane potential ( $V_m$ ) will be equal to the Nernst Potential for  $K^+$  ( $E_K$ )
- When the membrane is permeable only to  $Na^+$ , the membrane potential ( $V_m$ ) will be equal to the Nernst Potential for  $Na^+$
- When the membrane is permeable to both  $K^+$  and  $Na^+$ , then  $E_K < V_m < E_{Na}$

65 45

The resting membrane is about 20 times more permeable to  $K^+$  than to  $Na^+$

This is why the *resting membrane potential* is close to  $E_K$

The *Goldman Equation* is a way of understanding the relative influences of several, physiologically-important, ions in maintaining the *Resting membrane potential*

$$V_m = \frac{RT}{F} \ln \left[ \frac{P_K[K^+]_o + P_{Na}[Na^+]_o + P_{Cl}[Cl^-]_i}{P_K[K^+]_i + P_{Na}[Na^+]_i + P_{Cl}[Cl^-]_o} \right] \text{ Goldman Eqn}$$

*permeability favours the ions absent from the cell.*

In= natural logarithm (log to base e)

R= The Gas constant

T= temperature in degrees Kelvin

F= The Faraday constant

P<sub>Cl</sub>= membrane permeability to chloride ions

[Cl<sup>-</sup>]<sub>i</sub>= Concentration of chloride ions inside the cell

### Learning objectives: Resting Membrane potential

- 1.1 Describe the characteristic arrangement of the soma, axon, dendrites and axon terminal of a somatic motor neuron and explain the roles that these structures play in the function of the neuron.
  
- 1.2 Explain what is meant by the electrochemical (Nernst) equilibrium for an ion. What forces contribute to it?
  
- 1.3 If the temperature were to rise how would this affect the magnitude of the Nernst Potential for potassium?
  
- 1.4 Referring to the concentration gradient and the forces that act on K<sup>+</sup> under different conditions, explain why the Nernst potential for K<sup>+</sup> is normally negative.

$$E_K = \frac{RT}{2F} \ln \left[ \frac{[K^+]_o}{[K^+]_i} \right],$$

$$K^+ \ll K^+_i, \therefore \ln \left[ \frac{[K^+]_o}{[K^+]_i} \right] \approx 0.$$

## Learning objectives: Resting Membrane potential (cont)

1.5 Referring to the concentration gradient and the forces that act on  $\text{Na}^+$  under different conditions, explain why the Nernst potential for  $\text{Na}^+$  is normally positive.

$\text{Na}^+$  more abundant inside,  $\therefore$  it is

1.6 Referring to the concentration gradient and the forces that act on  $\text{Cl}^-$  under different conditions, explain why the Nernst potential for  $\text{Cl}^-$  is normally negative.

$\text{Cl}^-$  more abundant outside due to the gradient.

1.7 Suppose that in an animal from the planet Zeta the neurons contain a much higher concentration of  $\text{Ba}^{2+}$  ions in their cytosol than in the extracellular fluid. Suppose there are also  $\text{Ba}^{2+}$ -selective channels in the neuron membrane. Will the Nernst Potential for  $\text{Ba}^{2+}$  be positive, negative or zero? What if the membranes had no permeability to  $\text{Ba}^{2+}$ ?

$$\text{Ba}^{2+}_o \neq \text{Ba}^{2+}_i$$

$$E_{\text{Ba}^{2+}} = \frac{RT}{2F} \ln \left[ \frac{(\text{Ba}^{2+})_o}{(\text{Ba}^{2+})_i} \right]$$

$\therefore E \neq 0$ .

no permeability,

## Learning objectives: Resting Membrane potential (cont)

1.8 In what way would a doubling of the density of potassium leakage channel be expected to affect the Resting membrane potential for potassium of the cell in question? Would it alter the Nernst Potential?

*• would not alter  $V_m$ ,  
• would bring  $V_m$  closer to  $E_{\text{K}^+}$*

1.9 Considering what we have learnt about the Nernst Potentials for  $\text{Na}^+$  and  $\text{K}^+$ , and assuming the membrane contains ion channels that are permeable to both of them, explain how ongoing diffusion of each of these ions would collectively help maintain the Resting membrane potential.

*buffering, .*

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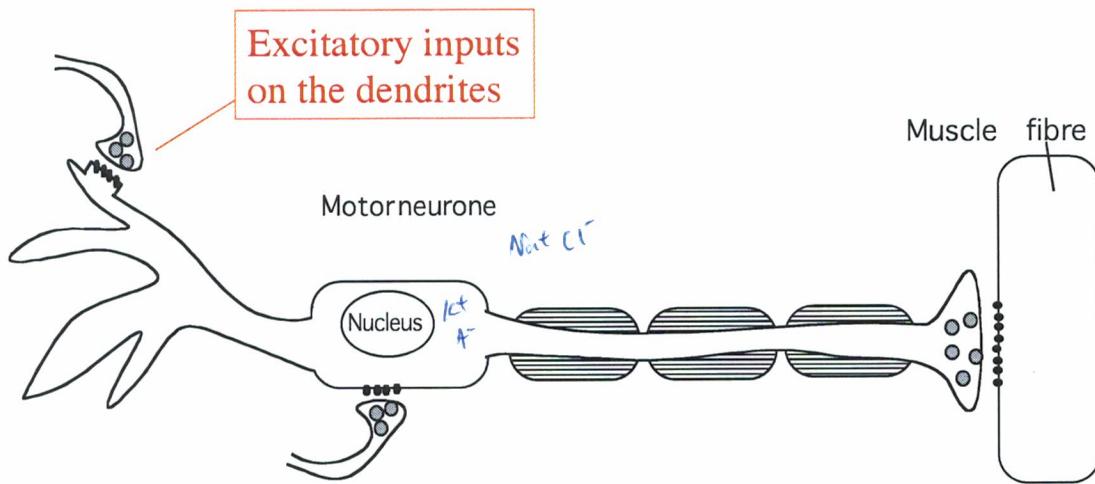
Cellular Neurophysiology Lect. 2 -Dr Bill Phillips, Dept of Physiology

## The Action Potential

28/3/15

- Need for amplified signalling
- Depolarisation initiates neuronal signalling
- Voltage gated sodium channels & the Hodgkin Cycle
- Voltage gated potassium channels and repolarisation
- Ratio of permeability: potassium and sodium ions
- $\text{Na}^+$  Channel inactivation and the refractory period
- Information is encoded in by AP frequency
- Role of the  $\text{Na}^+/\text{K}^+$  Pump in nerve signalling

## Need for amplified signalling

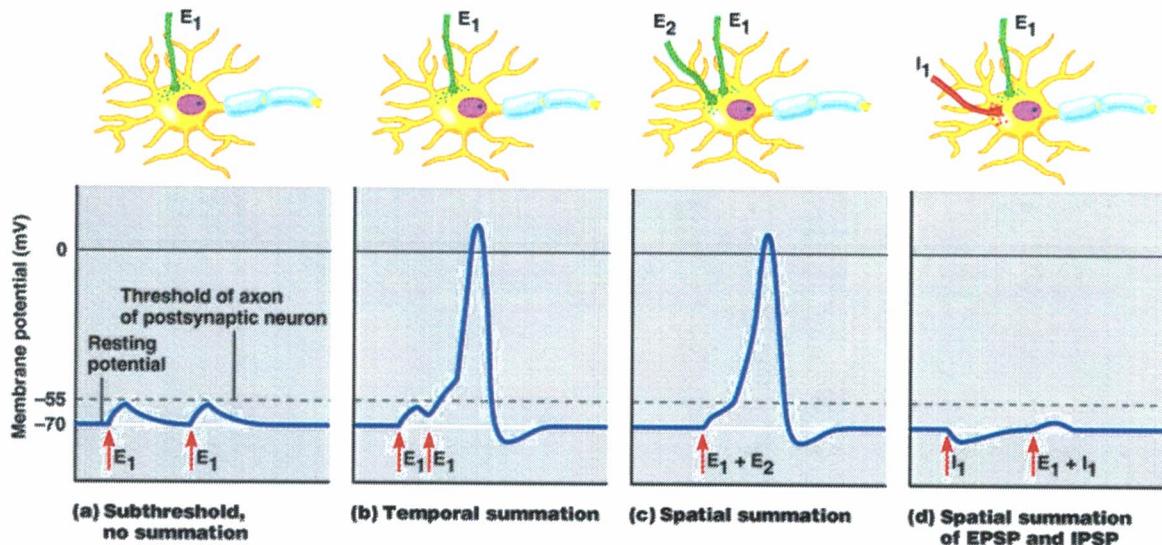


ventral spinal cord. controlling motoneurone = controlling muscle fibre.  
signals need to be amplified while passing through.  
→ Signals need to pass fast, large distances at more  
↓ destructions  
→ AP is non-linear, below threshold will not cause  
further propagation.

## Depolarisation initiates neuronal signalling

- Membrane is depolarised when there is a net inward current  
*membrane potential rises.*
- Depolarisation is usually initiated by opening of ligand gated cation channels at an excitatory synapse
- Depolarisation can also be triggered artificially, say by applying an electrical stimulus (Prac class)

# Depolarisation initiates neuronal signalling

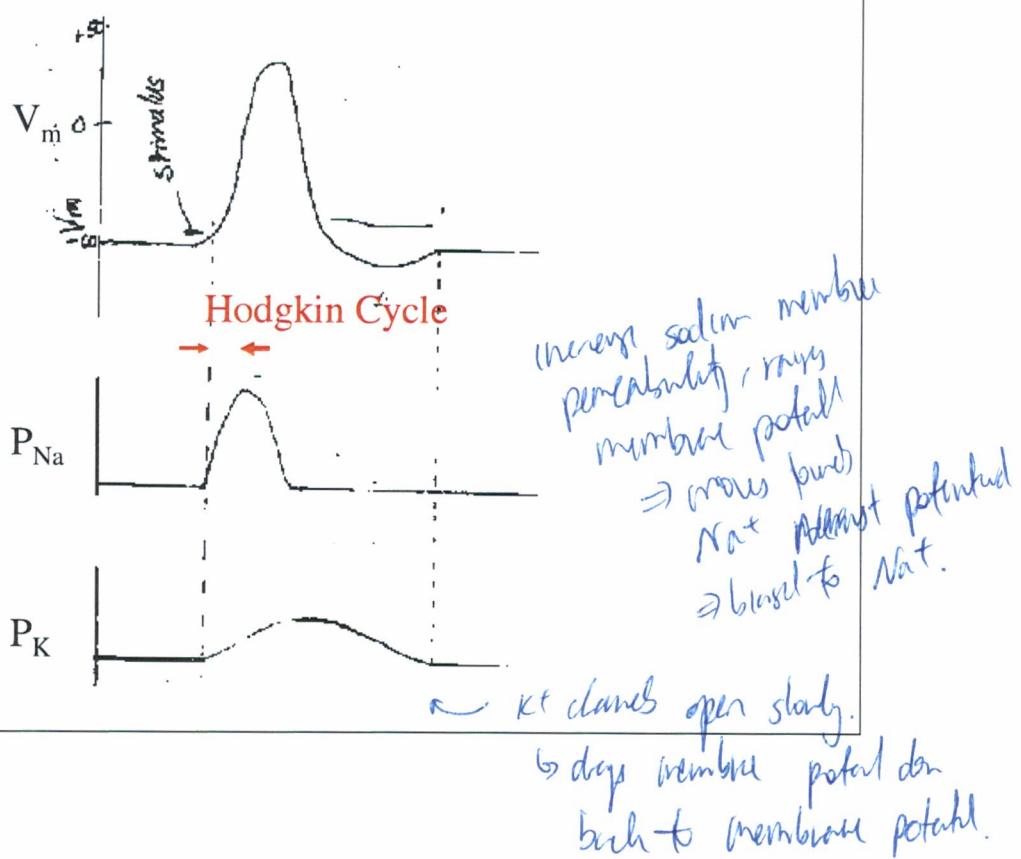


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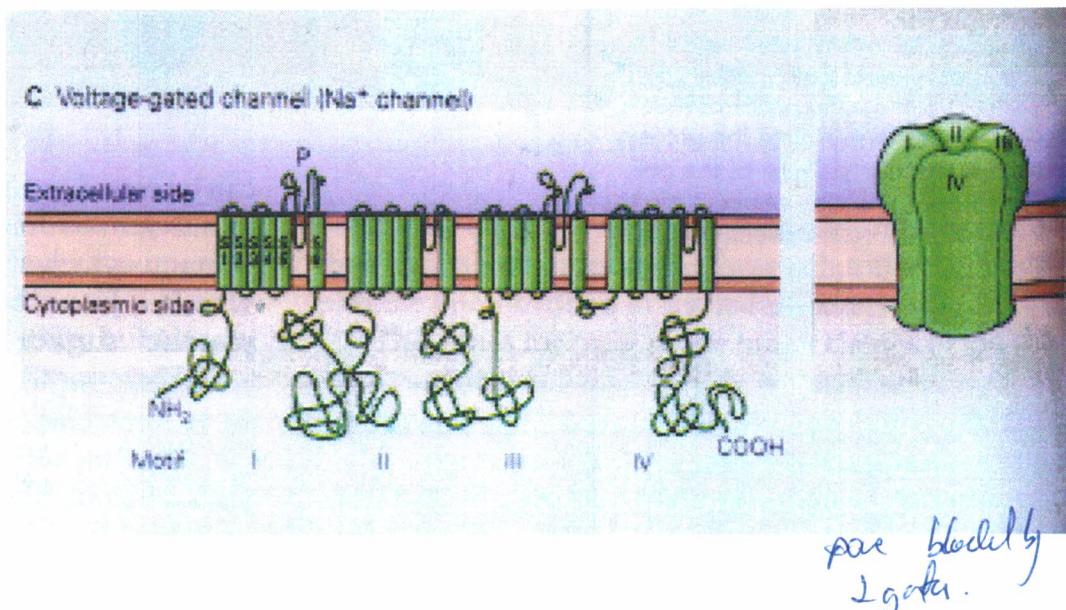
Fig 11.21 From Human Anatomy & Physiology by Marieb, E.N. 6th Edn

$E_1$  is synaptic input.  $\Rightarrow$  triggers the AP.  
 $E_2$ .

## Voltage gated sodium channels



# Voltage gated sodium channels



Principles of Neural Science 4th Edn Kandel et al. ©2000 McGraw Hill

## Voltage-gated sodium channels

- Closed when the membrane is polarised (activation gates).
- Begin to open as the membrane depolarises
- Selectively permeable just to  $\text{Na}^+$
- Begin to inactivate as the membrane depolarises
- Inactivation shuts off the  $\text{Na}^+$  current flow
- ‘voltage gates’ and ‘inactivation gates’

shuts off channel, prevents  
ions flow

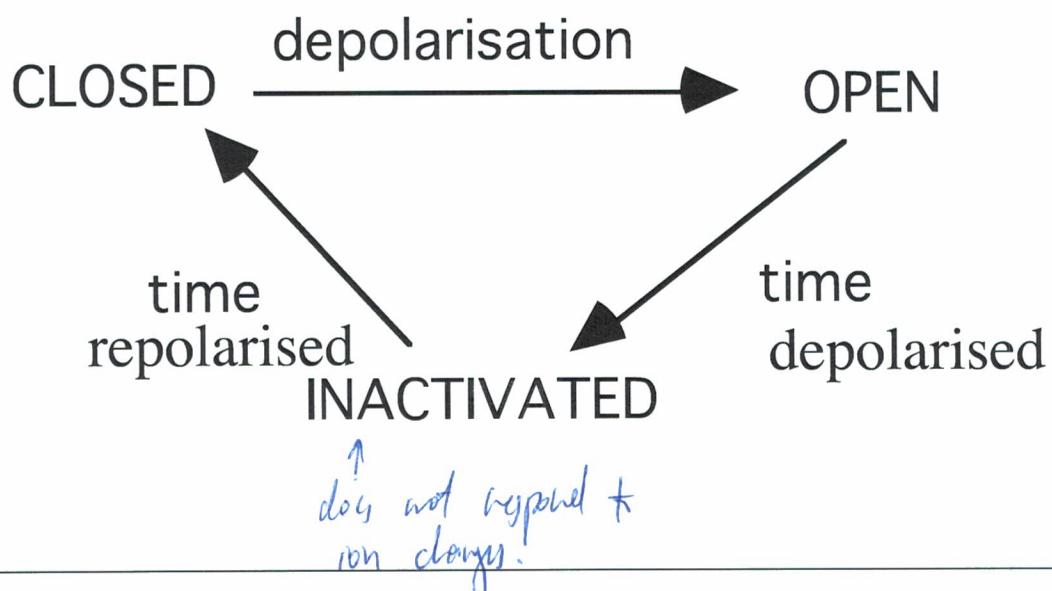
is contributed to lack of overshoot AP.

# Hodgkin Cycle

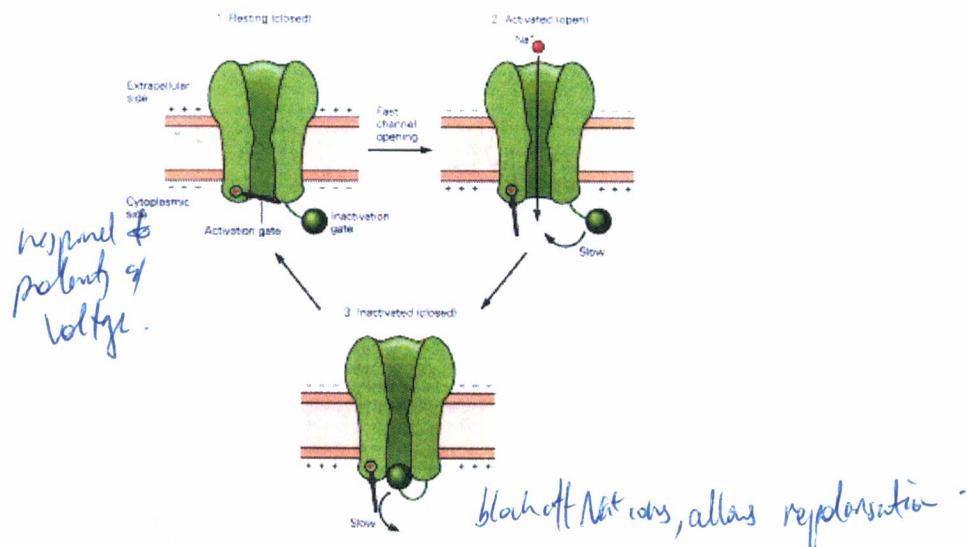
- Stimulus depolarisation opens a small fraction of voltage-gated  $\text{Na}^+$  channels
- Increase in inward current through these  $\text{Na}^+$  channels further depolarises the membrane
- As membrane depolarises more, a greater fraction of the  $\text{Na}^+$  channels open leading to more depolarisation etc

*membrane potential & permeability goes rapidly up.*

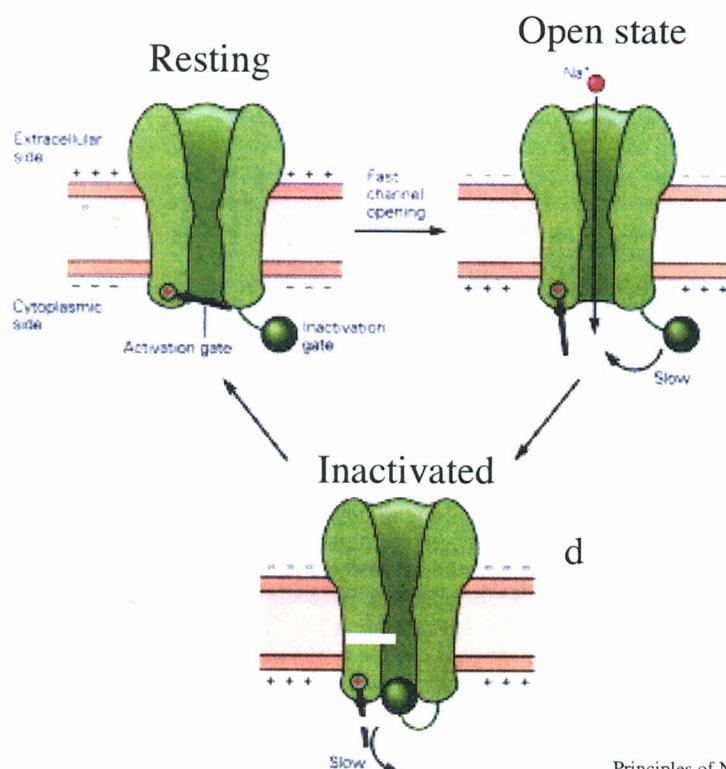
Voltage-gated  $\text{Na}^+$  channels can exist in multiple states depending upon the recent history of depolarisation



# 'voltage gates' and 'inactivation gates'

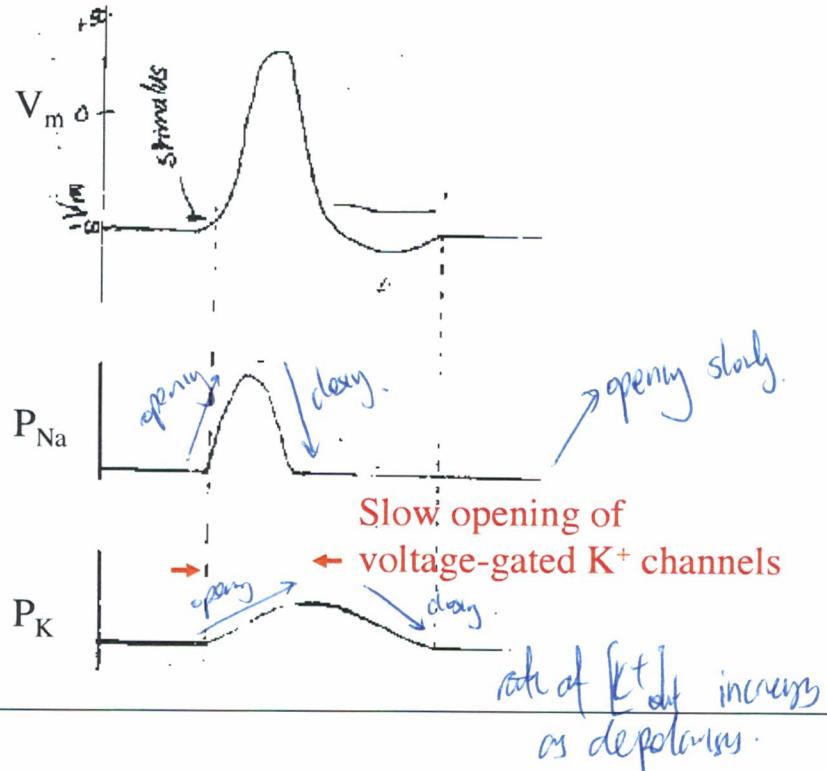


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## Voltage gated potassium channels

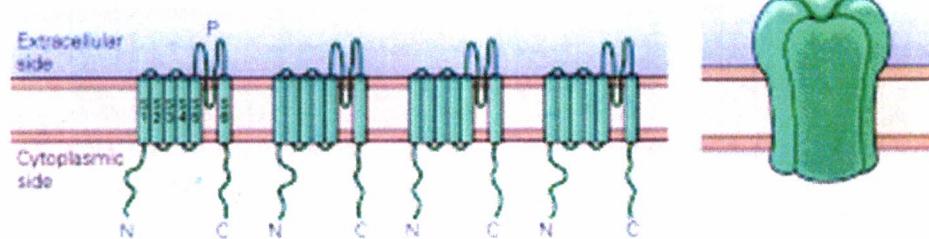


## Voltage-gated potassium channels

- Mostly closed when the membrane is polarised
- Begin to open as the membrane depolarises
- Do not inactivate
- Fraction of channels open increases proportionately with depolarisation

# Voltage gated potassium channels

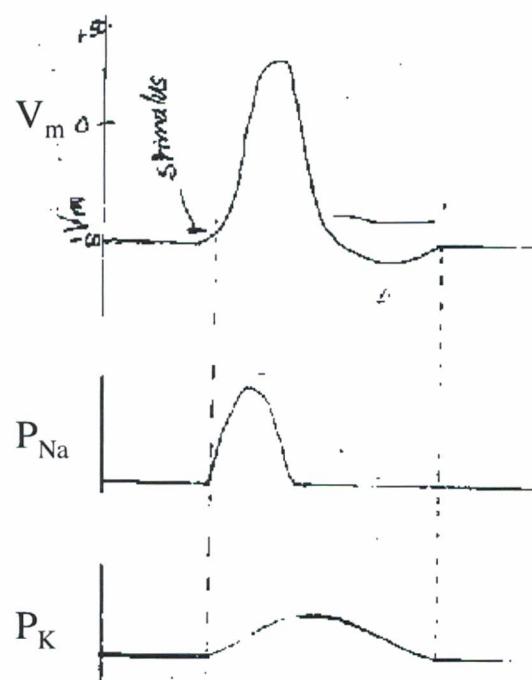
A Voltage-gated K<sup>+</sup> channel



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10s work.  
100s muscle.

## Relative permeability



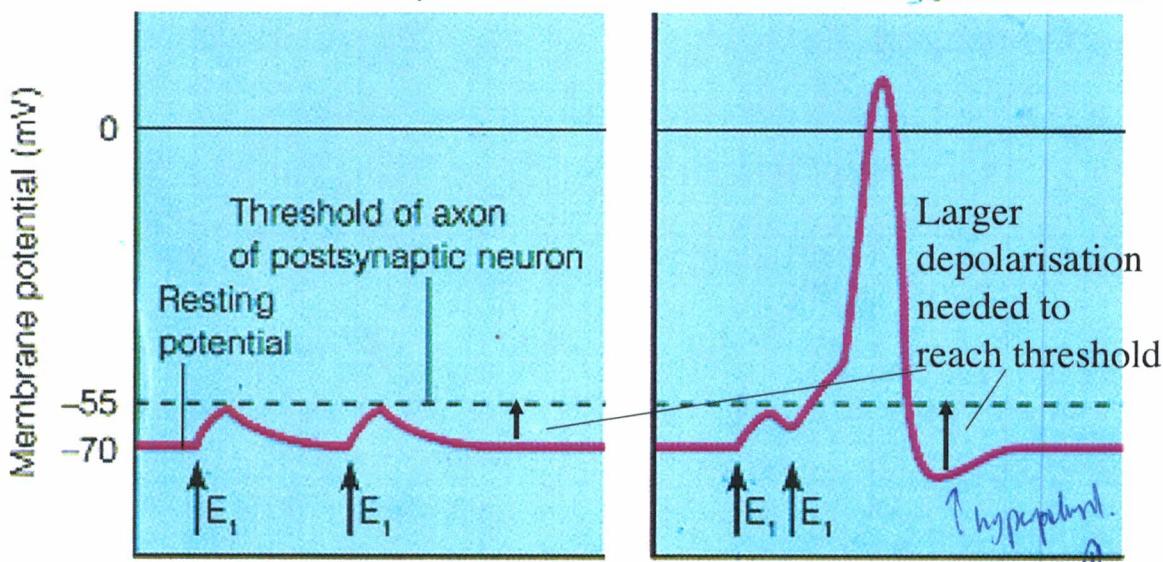
## Change in Ratio of permeabilities:

- Stimulus begins to open voltage-gated  $\text{Na}^+$  channels
- If sufficient, the Hodgkin Cycle begins
- As the membrane rapidly depolarises further,  $\text{Na}^+$  channels begin to inactivate and  $\text{K}^+$  channels begin to open
- Shutting off of the inward  $\text{Na}^+$  current and increase in the outward  $\text{K}^+$  current repolarises the cell

## Limits to Action Potential Frequency

- Voltage-gated  $\text{Na}^+$  channels stay inactivated for a fraction of a millisecond after the action potential preventing a second AP
- After the action potential there is a brief hyperpolarisation (period of reduced excitability). Effect?

**Period of Reduced Excitability: The After-Hyperpolarisation** following the action potential means that it is less likely that an action potential will be triggered

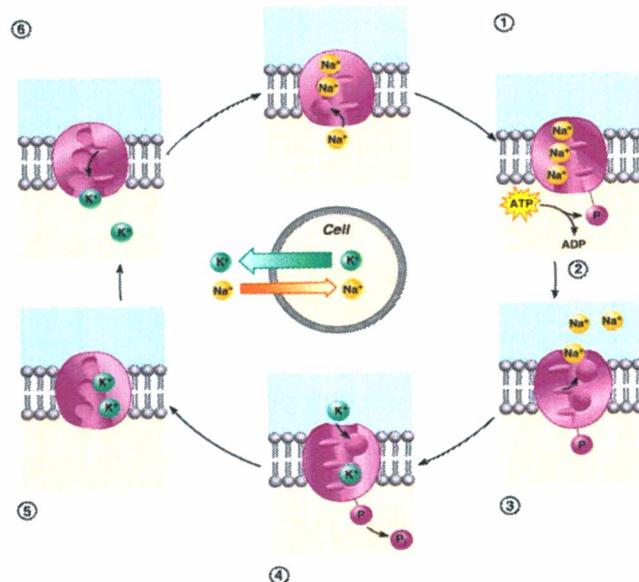


From Human Anatomy & Physiology by Marieb, E.N. ©2001 Addison Wesley & Longman

## Information is encoded by AP frequency

- When they become depolarised most neurons fire a 'train' of several to hundreds of action potentials (spikes)
- The frequency of spikes within a trains usually encodes the intensity of the sensation or instruction
- Trains of spikes are usually interspersed by periods of silence

## Role of the Sodium Potassium Pump ( $\text{Na}^+/\text{K}^+$ ATPase) in neuronal signaling?



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From Human Anatomy & Physiology by Marieb, E.N. 6th Edn

predicts the concentration gradient.

$$[\text{K}^+]_{\text{i}} \gg [\text{K}^+]_{\text{o}}$$

$$[\text{Na}^+]_{\text{i}} \ll [\text{Na}^+]_{\text{o}}$$

primary active transport  
works slowly.

$\Rightarrow$  works slowly.

The Resting membrane potential:

role of the electrogenic  $\text{Na}^+/\text{K}^+$ -pump versus (pumps 3  $\text{Na}^+$  out of the cell for every 2  $\text{K}^+$  into the cell)

versus

the Diffusion potential hypothesis: what I have taught you

membrane slowly  
hypothetical  
 $\text{Na}^+/\text{K}^+$ -atpase

stops working

In what way does the electrogenic  $\text{Na}^+/\text{K}^+$ -pump influence the resting membrane potential?

Testing the hypothesis- What happens if the pump is blocked:

- Immediate effect: resting membrane potential was reduced by about 20% (membrane still polarized but slightly less so)
- After about 20min: further slow progressive run down of the resting membrane potential due to reduced potassium concentration gradient

## Learning Objectives: The action potential

- 2.1 Considering the role of ion-selective channels, explain why the resting membrane potential for most neurons is in the negative range of about -50mV to -80mV. Why isn't it positive? What factors might explain why electrophysiologists find differences among neurons in their resting membrane potentials?
- 2.2 If  $\text{Na}^+/\text{K}^+$ -pump is inhibited with a drug the resting membrane potential of the neuron decays only very slowly (over a period of about 20min) during which time action potentials can still be propagated in the neuron. What does this tell us about the role of the  $\text{Na}^+/\text{K}^+$ -pump in neuronal signalling?

## Learning Objectives: The action potential (cont)

- 2.3 Describe the functional differences between non-gated, ligand-gated and voltage-gated ion channels.
- 2.4 What is meant by Depolarised? Hyperpolarised? Threshold potential?
- 2.5 Describe the changes in membrane permeability that occur when the membrane of a neuron is depolarised to threshold, and how they produce the subsequent changes in membrane potential that we refer to as the action potential.
- 2.6 What are the two types of gates on the voltage-gated sodium channel in the axon membrane? Under what circumstances do each of these gates open?

## Learning Objectives: The action potential (cont)

2.7 Describe what is meant by the term Hodgkin Cycle.

Precisely how would a small reduction in the density of voltage-gated sodium channels in the axon membrane be expected to affect membrane depolarisation during the Hodgkin cycle?

2.8 What are the ion conductive and gating properties of the voltage-gated potassium channel in the axon membrane? How does its properties as a channel differ to those of the voltage-gated sodium channel?

## Learning Objectives: The action potential (cont)

3.9 In what way would a reduction in the density of voltage gated potassium channels in the membrane be expected to alter the repolarisation of the axon after an action potential? Why?

3.10 How do the inactivation properties of the voltage gated  $\text{Na}^+$  channels relate to the maximum frequency of nerve signalling?

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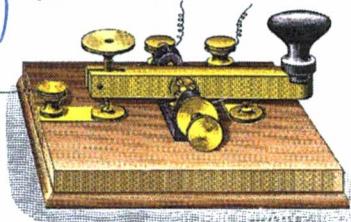
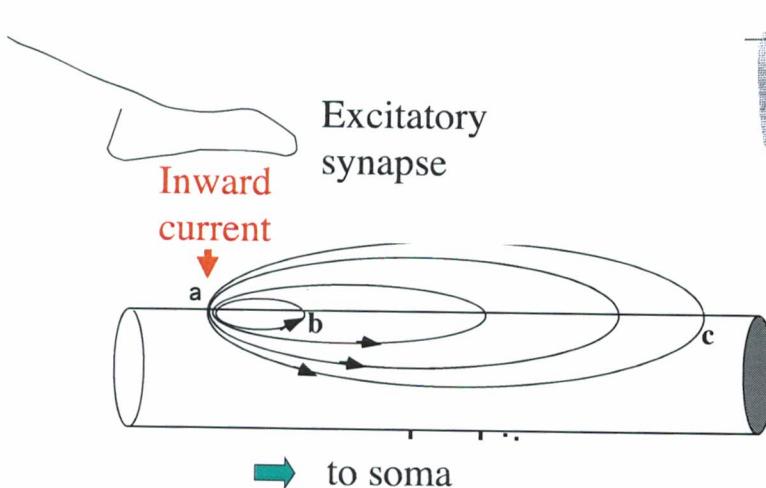
Cellular Neurophysiology Lecture 3 Dr Bill Phillips

## Action Potential propagation

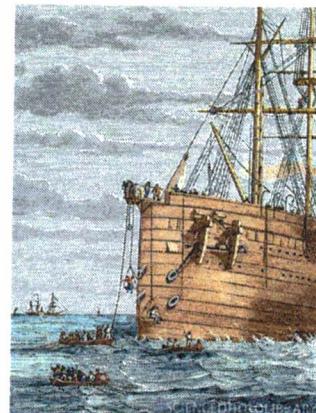
28/3/15

- Cable theory allows us to understand the limitations on signal transmission in axons
- Passive electrical properties of axons slow action potential propagation
- Continuous Propagation of action potentials
- Saltatory Propagation
- Damage to the myelin sheath modifies saltatory propagation in predictable ways

diminishes in amplitude as it moves along the axon.



Artwork from A Travers l'Electricite  
(G. Dary, Paris, 1900)



Dendrites and axons are long, thin tubes that behave like a long, thin, insulated underwater cable

A tube surrounded by insulation with insides inside

↳ there is resistance to flow of current

outside has less resistance outside than inside

→ copper wires surrounded by → understandably becomes slowly bad helium.

La Telegraphie Historique (History of Telegraphy)  
by Alexis Belloc 1888.

The membrane has electrical properties that slow the spread of changes in membrane potential

Membrane has electrical capacitance (stores charge)

electrostatic attraction

capacitor

lipid bilayer is a capacitor.



Ion channels in the membrane have resistance but allow leakage of local circuit currents out of the membrane

Ion channels spread across membrane

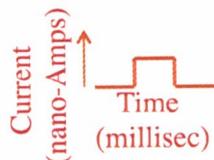
resistance

The axoplasm is narrow and has resistance impedes the depolarising current down the membrane



An electrical equivalent circuit model for understanding the spread of signals along the membrane

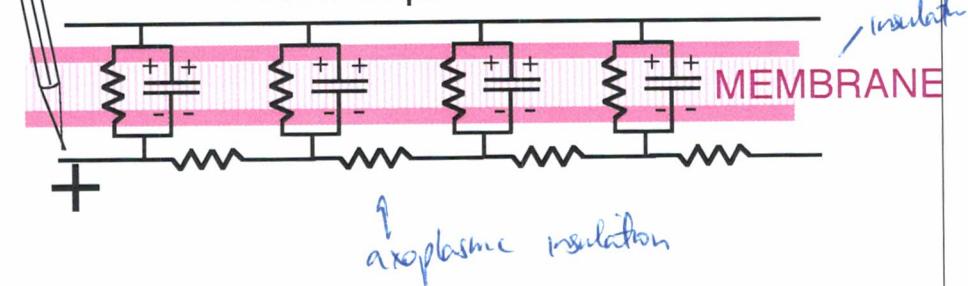
Experimental stimulus



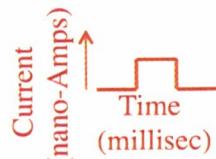
Device to inject current

no resistance.

Axon Equivalent circuit



Experimental stimulus

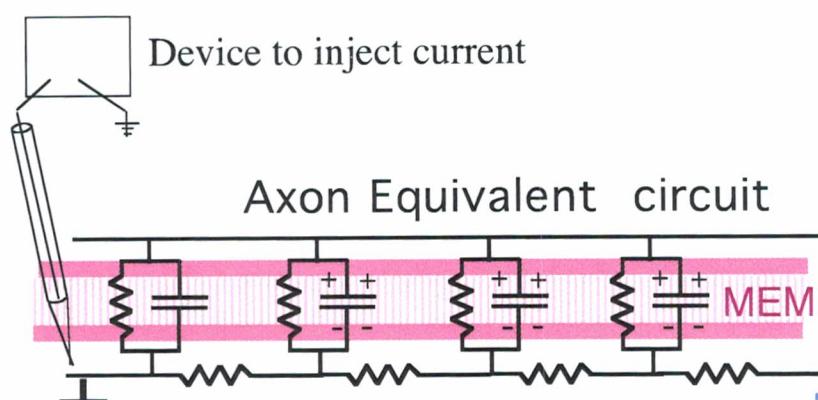


Device to inject current

Membrane response

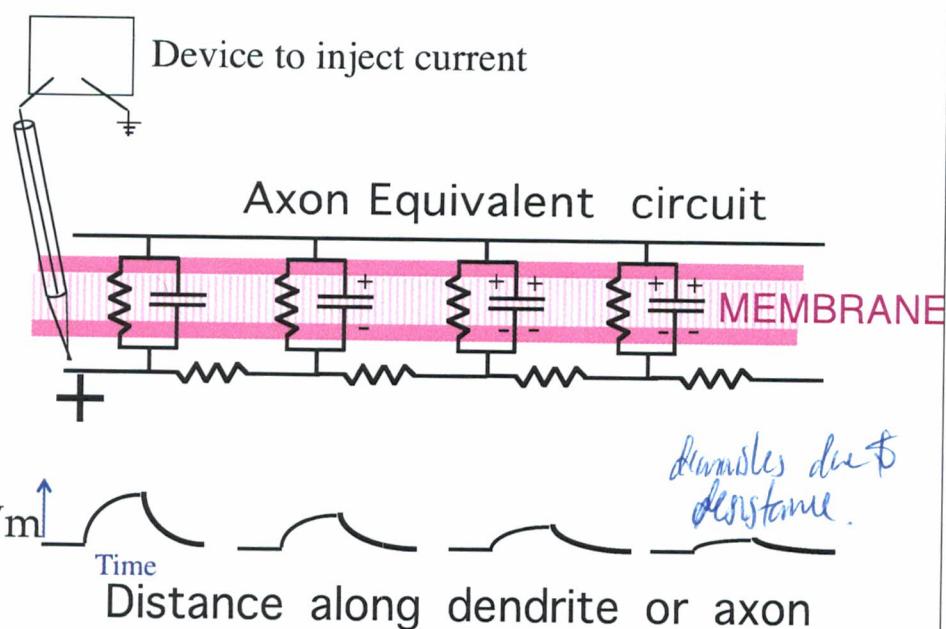
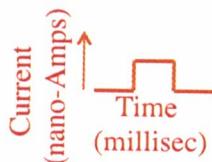


Axon Equivalent circuit



Membrane potential response declines with distance from the site of the depolarising current

### Experimental stimulus



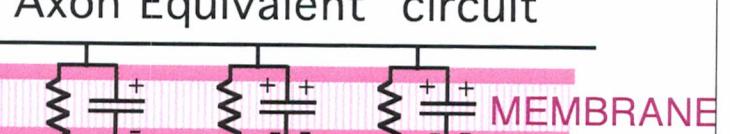
### Trigger Zone

$\text{Na}^+$

### Membrane response



### Axon Equivalent circuit



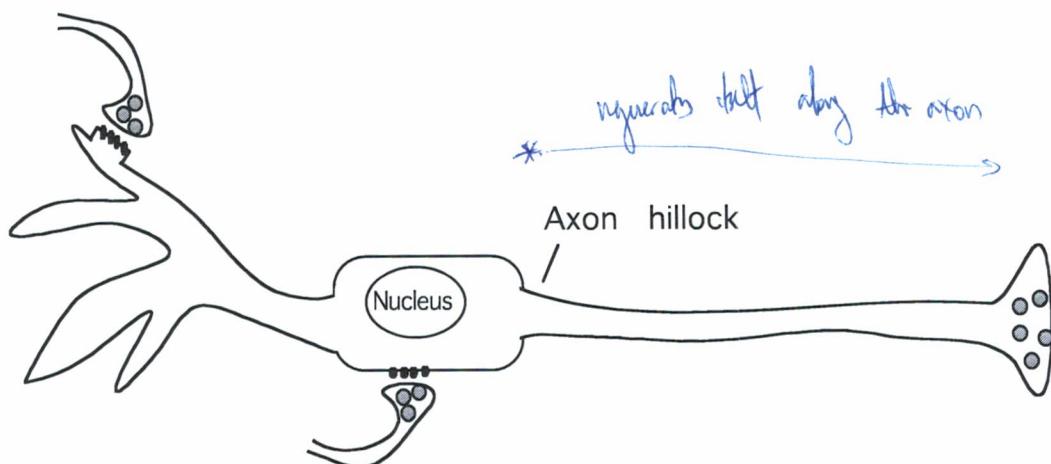
Distance along dendrite or axon

# Continuous propagation

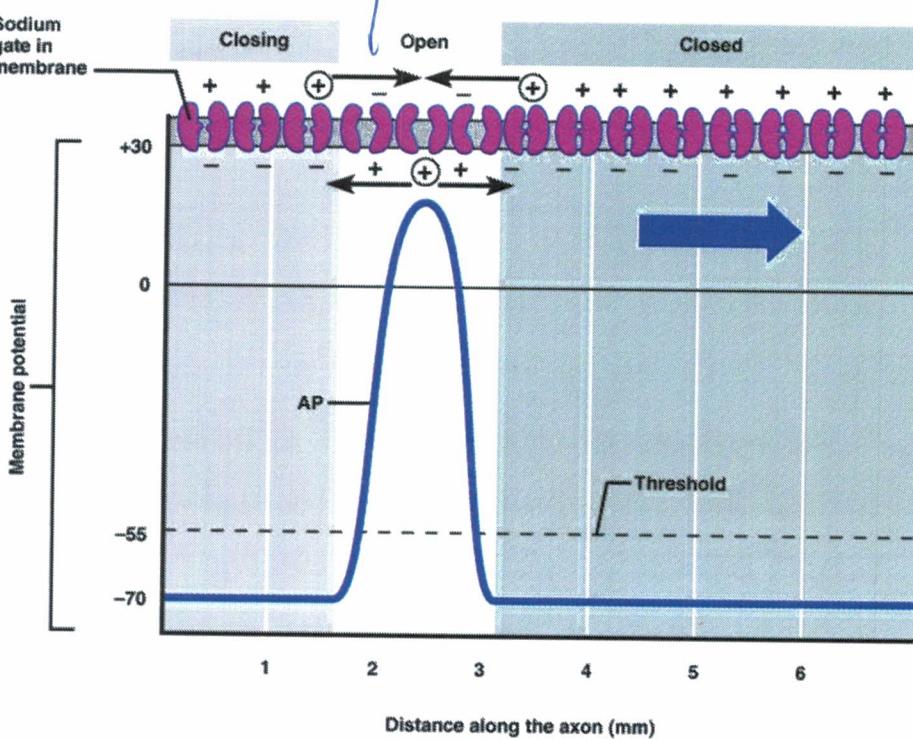
→ seen in spinal  
→ seen in pain  
sensation  
(slow sensation).

- The action potential normally starts at the axon hillock where the density of voltage-gated  $\text{Na}^+$  channels is high
- In non-myelinated nerves the action potential propagates continuously along the axons by sequentially activating populations of  $\text{Na}^+$  channels in adjoining segments of axon

## Continuous Propagation of the AP in non-myelinated nerve fibres



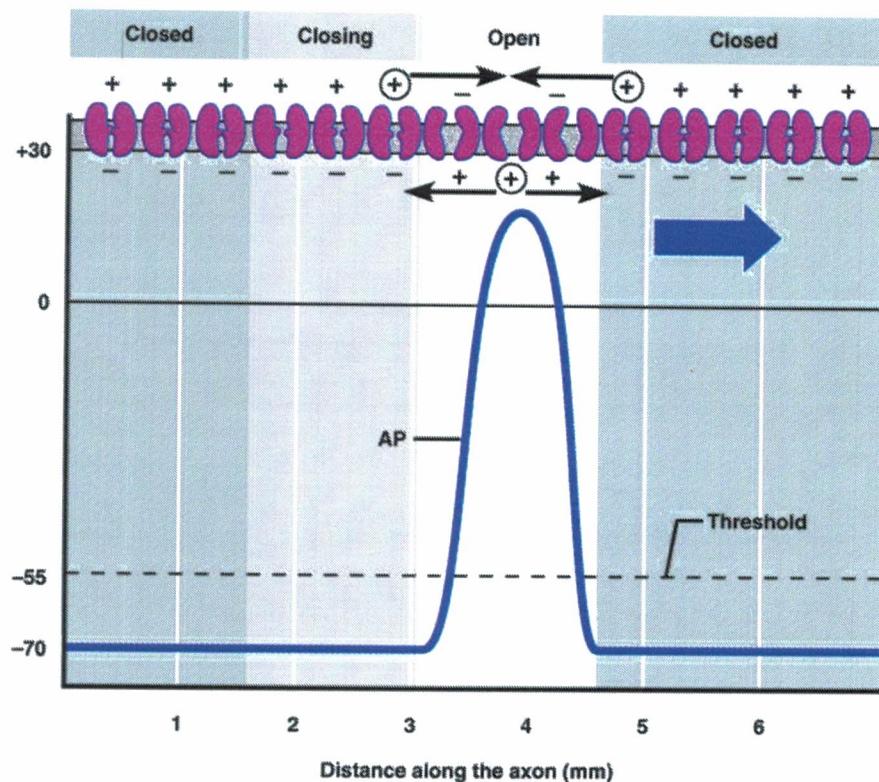
*local current. (conductor with local net excess positive charge)*



(a) Time = 0 ms

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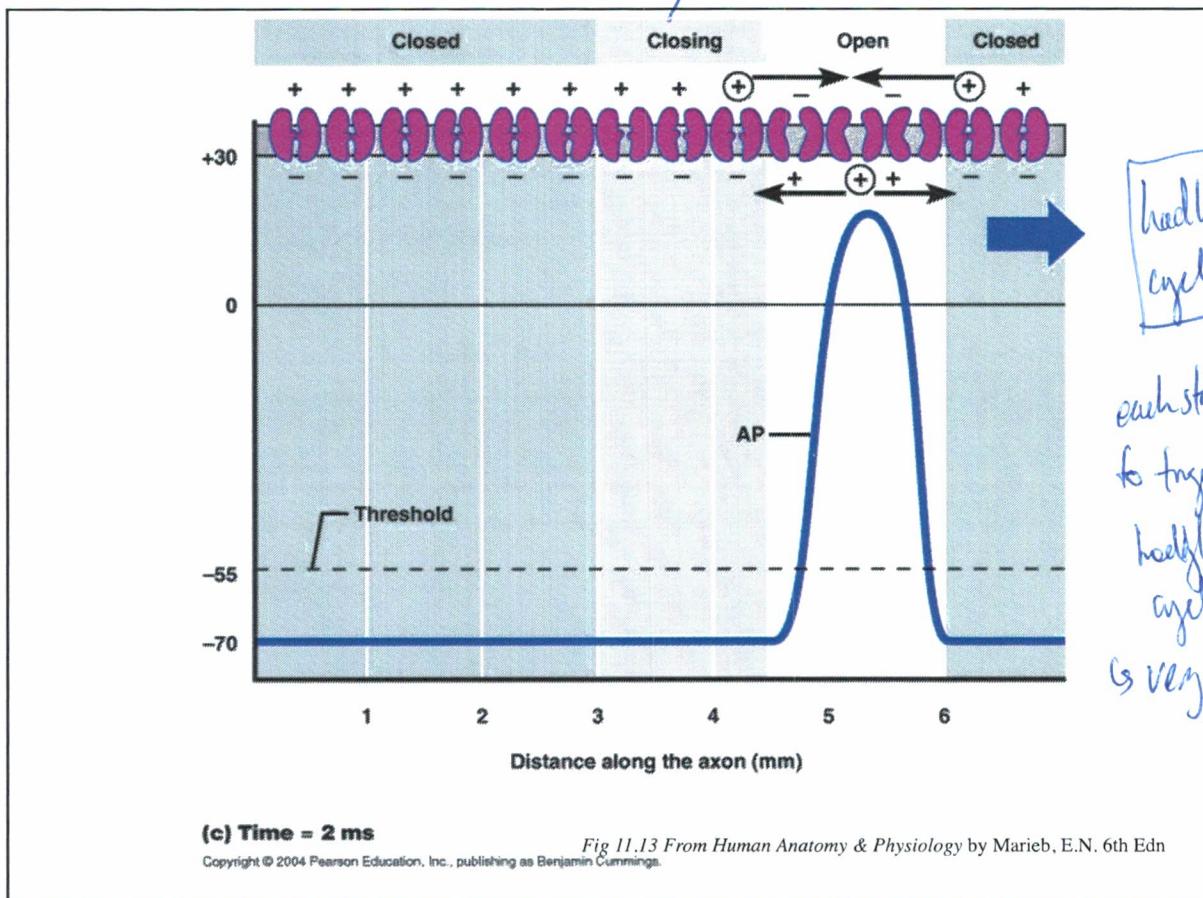
Fig 11.13 From Human Anatomy & Physiology by Marieb, E.N. 6th Edn



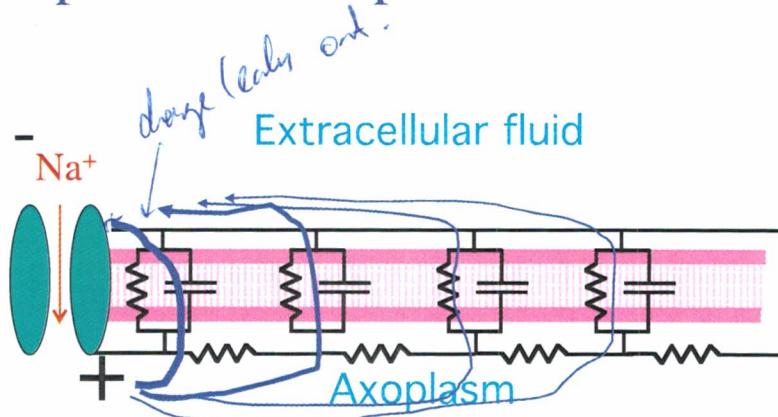
(b) Time = 1 ms

Fig 11.13 From Human Anatomy & Physiology by Marieb, E.N. 6th Edn

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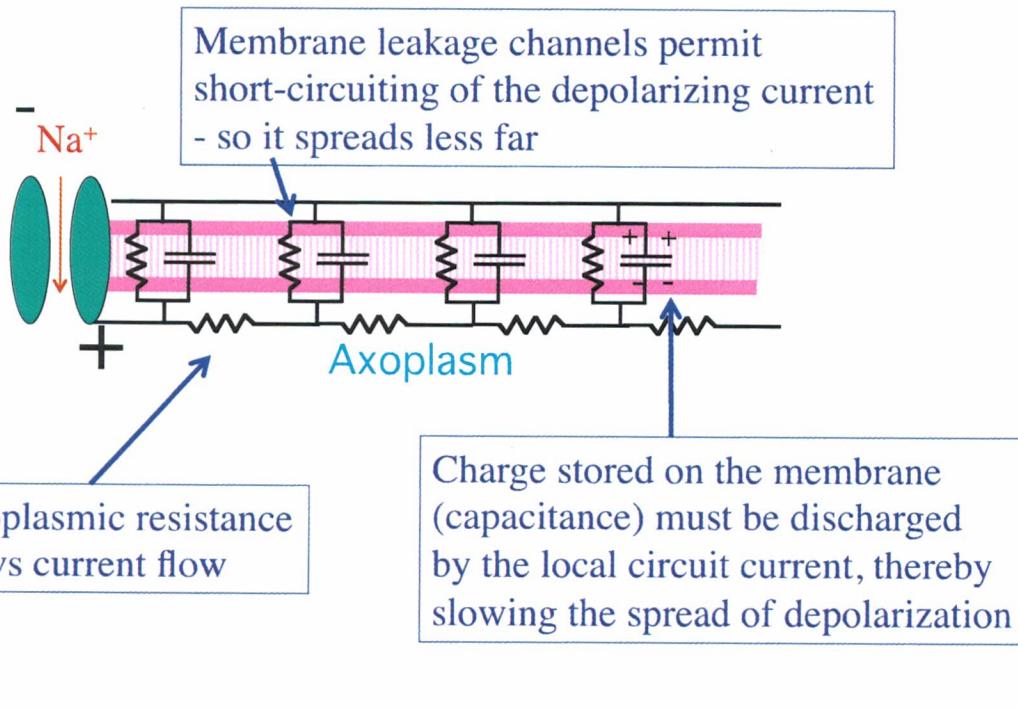


Local circuit (electrical) current flow  
Spreads the depolarization

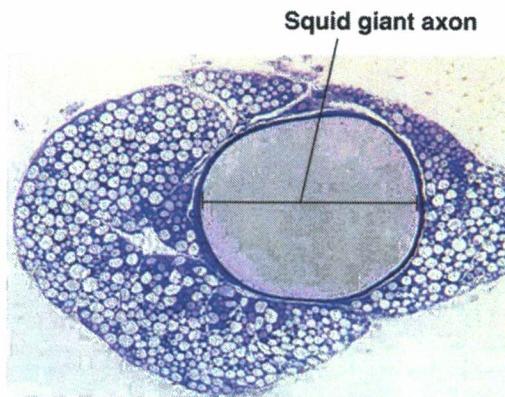


The electrical properties of the *equivalent circuit* components determine how far and how fast the depolarization will spread

Electrical properties determine the rate of spread of depolarization along the axon



**(a)** Large axons offer less resistance to current flow, but occupy space.

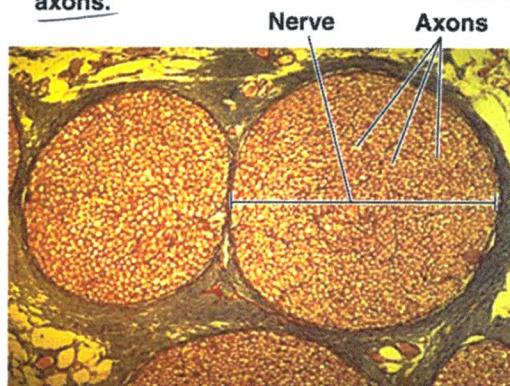


One giant axon from a squid

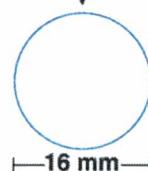
0.8 mm diameter

↳ Reduces resistance to conduction

**(b)** Small myelinated axons conduct action potentials as rapidly as large unmyelinated axons.



If 20 myelinated mammalian axons in the nerve above were each the size of a squid giant axon, the nerve would have to be this size.



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Figure 8-17 - Overview

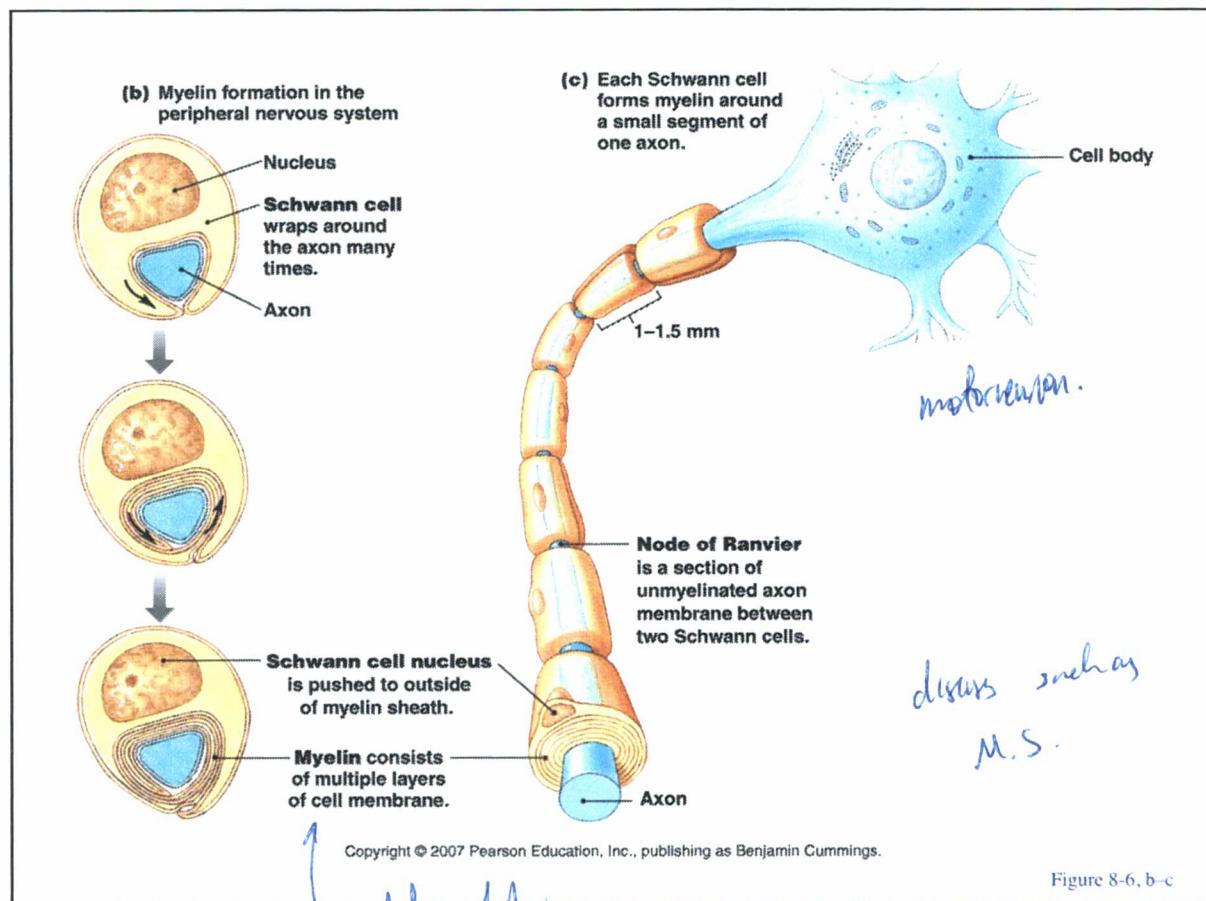
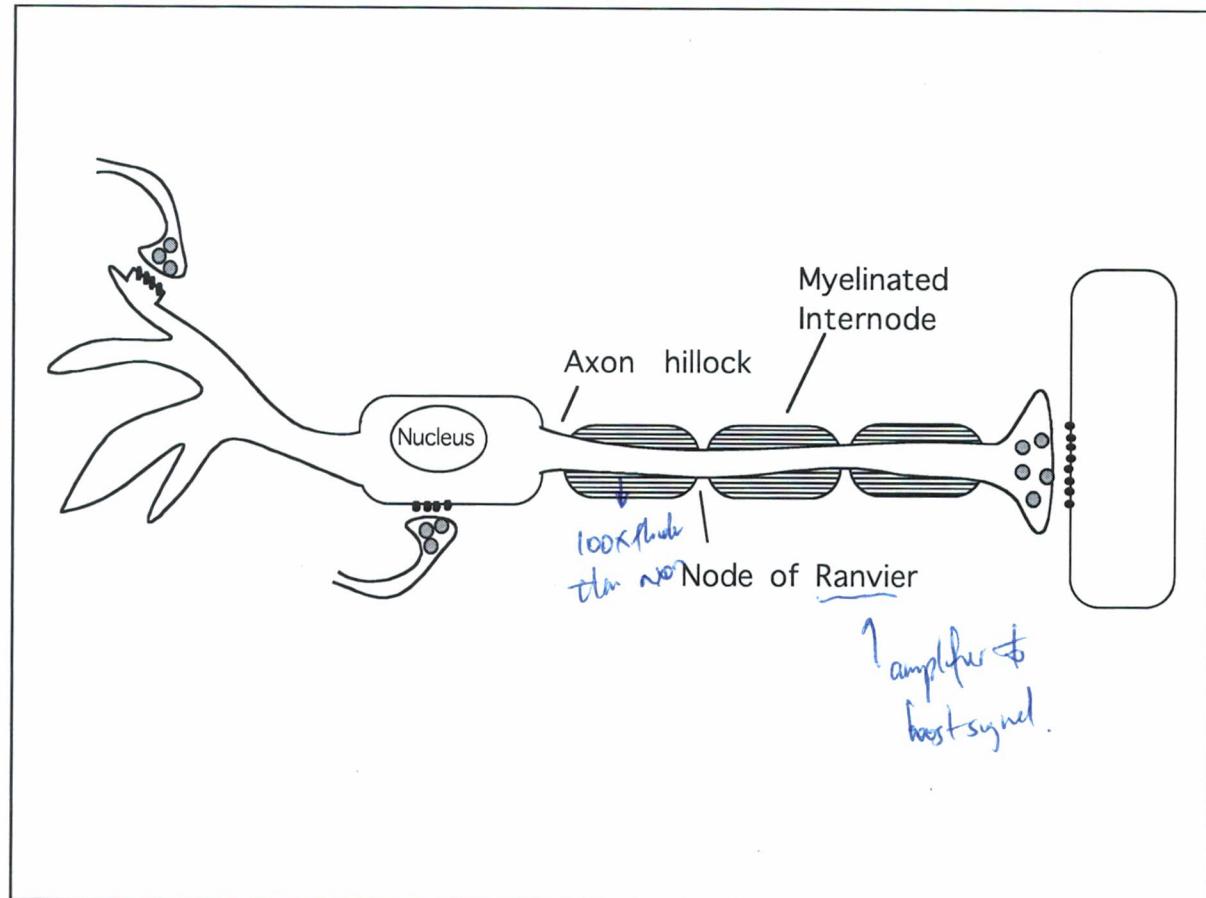


Figure 8-6, b-c

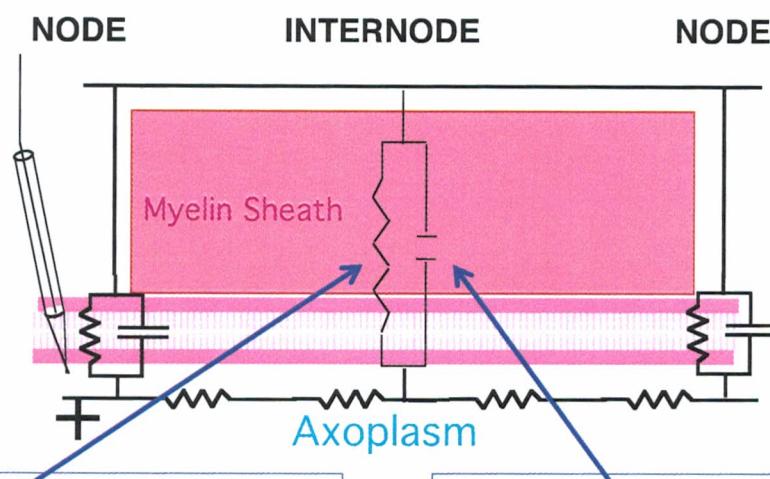
## Saltatory Propagation

- Adaptation to permit faster propagation
- Myelin internodes formed by glial (Schwann) cells wrapped around internode regions of axons (~0.2mm long)
- Inward current during the rising phase of the action potential creates “local circuits”
- Local circuits depolarise neighbouring “Node of Ranvier” stimulating regeneration of the action potential



## Altered electrical properties in the myelinated internode

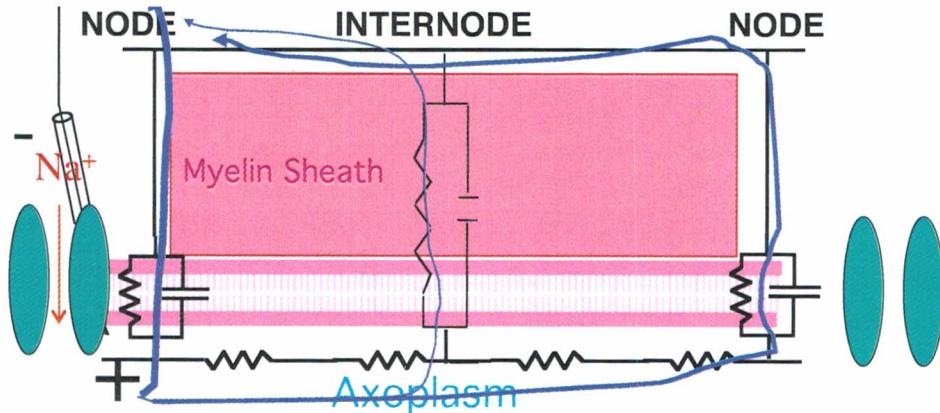
Extracellular fluid



The thick insulating myelin sheath increases *resistance of the membrane* to short-circuit currents

The thickened membrane is much less prone to hold charge (reduced *membrane capacitance*)

## Local circuit current flow in a myelinated axon



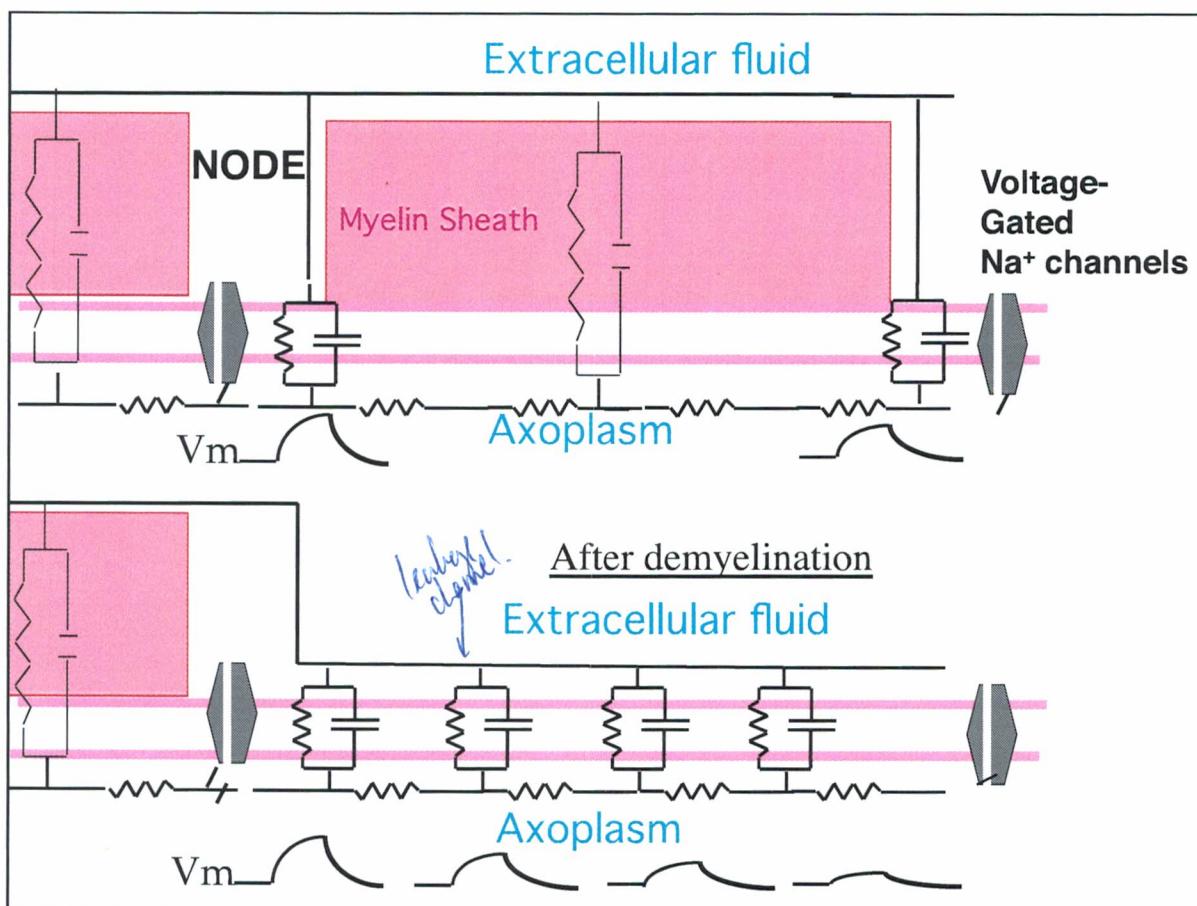
Local circuit current spreads passively from one Node to the next  
Initiating the Hodgkin Cycle at the next Node

### In saltatory propagation:

- Voltage-gated  $\text{Na}^+$  channels are concentrated at the axon hillock and Nodes of Ranvier
- The Hodgkin Cycle is triggered at one Node after another. This amplifies the signal.
- The signal travels passively as an electrical current between Nodes.
- The thick myelin insulation of the Internode allows the local circuit current to spread much further and faster than in un-myelinated fibres

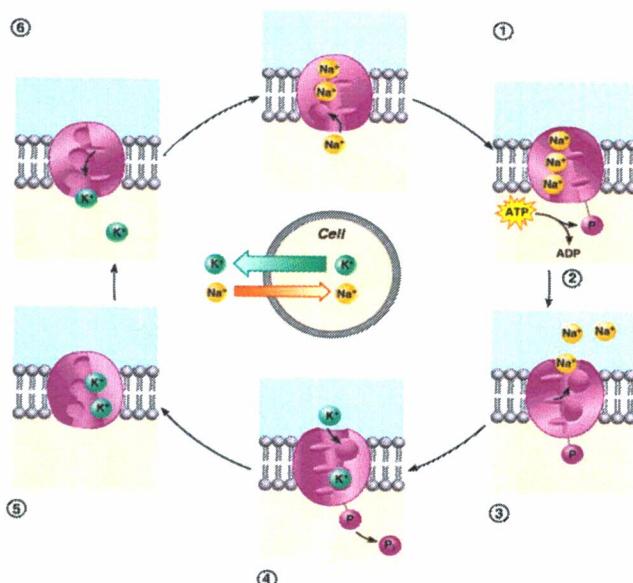
# Loss or myelin sheath (demyelination)

- Increases permeability of membrane to ions in the demyelinated internode regions
- Increased membrane capacitance in the denervated internode regions
- Reduced membrane electrical resistance leads to loss of amplitude of signal
- Inevitable slowing of action potential propagation through regions with high membrane capacitance.



## Role of the Sodium Potassium Pump (Na<sup>+</sup>/K<sup>+</sup> ATPase) in neuronal signaling?

→ maintain action potentials,  
but not used in generating them.



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From Human Anatomy & Physiology by Marieb, E.N. 6th Edn

## Learning objectives: Action Potential Propagation

3.1 What is meant by the term local circuit current?

Explain how local circuit currents spread the action potential along the axon membrane.

current inside the cell  
depolarizes channels  
of nodes of ranvier;  
allow influx & depol

3.2 What is meant by the axoplasmic resistance? Why does the diameter of the axon affect the <sup>to</sup> axoplasmic resistance? Are all axons the same diameter? If an axon is very thin, how would the spread of an action potential along it compare to a very large diameter axon?

less C → A more  
high resist & flow.  
slower

## Learning objectives: Action Potential Propagation

(cont)

extents much a neural  
elements & allows ions to  
cross-the membrane.

- 3.3 What is meant by the membrane conductance? What does it measure? What are the structures within the membrane that determines the membrane *conductance*? If an axon has a high membrane conductance, how would the spread of the action potential be affected, compared to an axon with low membrane conductance? Why?

~ spread slow.

ion leak channels.  
gated ion channels.

- 3.4 What do we mean by the electronics term “*capacitance*”? Why is electrical charge get stored on a membrane?

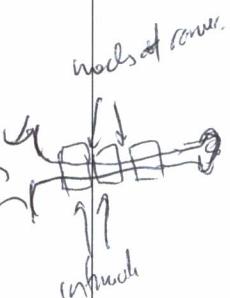
ability of a body to store charge.

## Learning objectives: Action Potential Propagation

(cont)

high capacitance =  
stores more charge  
on membrane  
charge per unit area.

- 3.5 In what way does the capacitance property of the lipid bilayer affect the rate of change of the membrane potential during electrical signalling in neurons?



- 3.6 Describe with the aid of a drawing how myelination modifies the structure of an axon. Label the *Nodes of Ranvier*, the *internode* regions and the location of voltage-gated sodium channels.

- 3.7 How is the capacitance per square cm of membrane affected by myelination of the membrane? Why is this?

reduced os & cap  
separat + & - dep  
on the membrane by  
voltage gated.

## Learning objectives: Action Potential Propagation (cont)

- 3.8 Describe two ways in which axons can become specialized in order to propagate action potentials more rapidly. In each case which passive electrical properties of the axon are modified: axoplasmic resistance? membrane conductance? membrane capacitance? How do these changes, in turn, speed up signalling?
- 3.9 With the aid of arrows on a diagram describe the differing paths taken by currents involved in the spread of an action potential along a myelinated axon and an unmyelinated axon.

1. myelinated axon = axolemma  
↓ axon  
↓ membrane capacitance  
↓ membrane conductance  
↓ axoplasmic resistance

2. unmyelinated axon = membrane of axolemma

## Learning objectives: Action Potential Propagation (cont)

- 3.10 Why is propagation of the action potential slowed down when axon tracts become demyelinated? Refer to the changes that occur in basic electrical properties and how these, in turn, affect action potential propagation.
- 3.11 Dendrites where synaptic inputs to a motor neuron arise are also very thin, tube-like structures, like axons. How would you expect this to affect the total amount of charge stored on the membranes of the dendritic tree? How would this affect the time-course of depolarising synaptic potentials arising from synapses on the dendrites?



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NMJ

PHSI2005/2905 Cellular Neurophysiology Lect. 4 - Dr Bill Phillips

↳ motoneuron &  
muscle.

Neuromuscular synaptic transmission 09/04/15

exocytosis, ligand-gated ion channel,  
packets & vesicles.

- *Recording postsynaptic electrical potentials*
- *The nicotinic acetylcholine receptor: example of a ligand-gated cation channel*
- *Pre-synaptic neurotransmitter release is controlled by calcium influx to the nerve terminal*
- *Quantal synaptic transmission*
- *Recycling of acetylcholine at the neuromuscular junction*

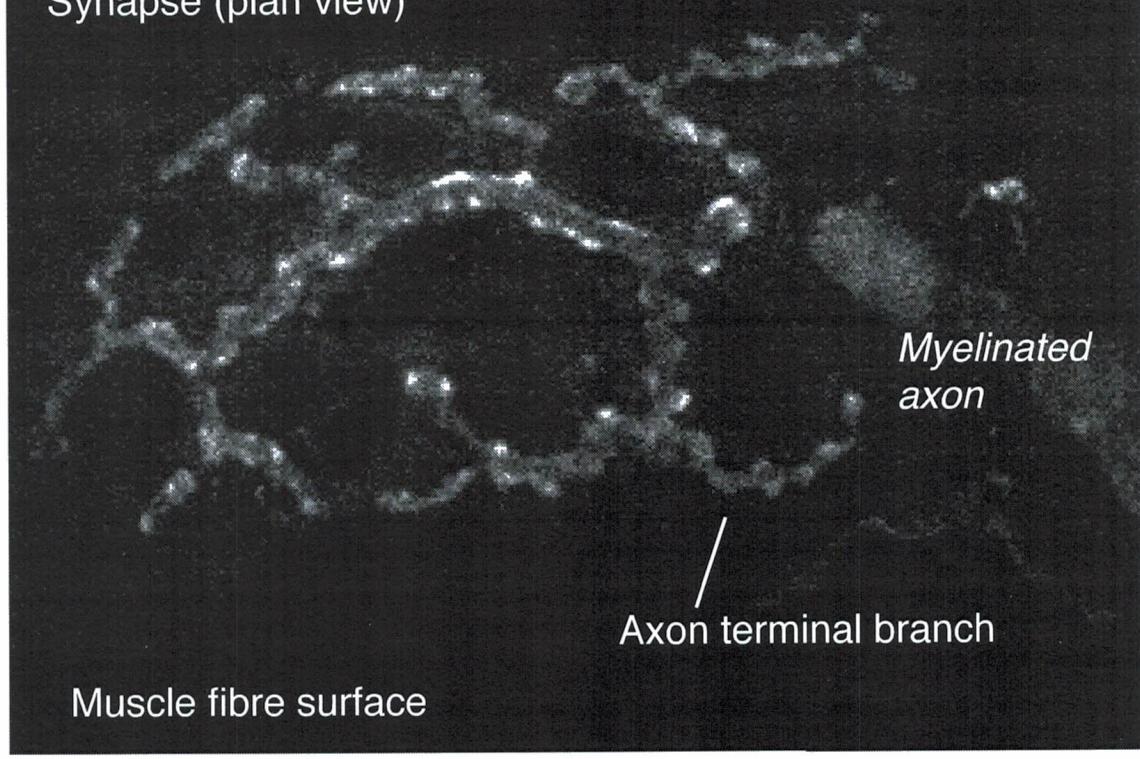
## Neuromuscular transmission: an example of *chemical synaptic transmission*

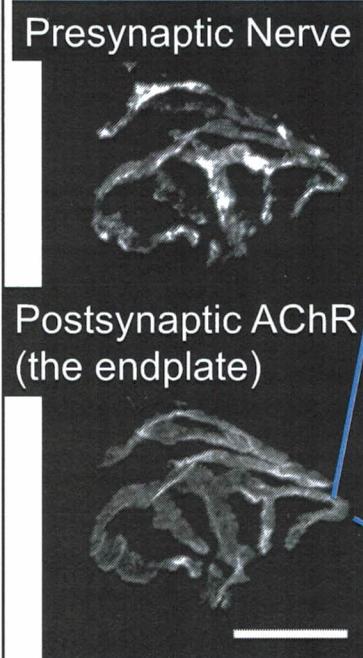
Overview of the steps involved:

so fat by transmission  
( $100\text{m}^{-1}$ )

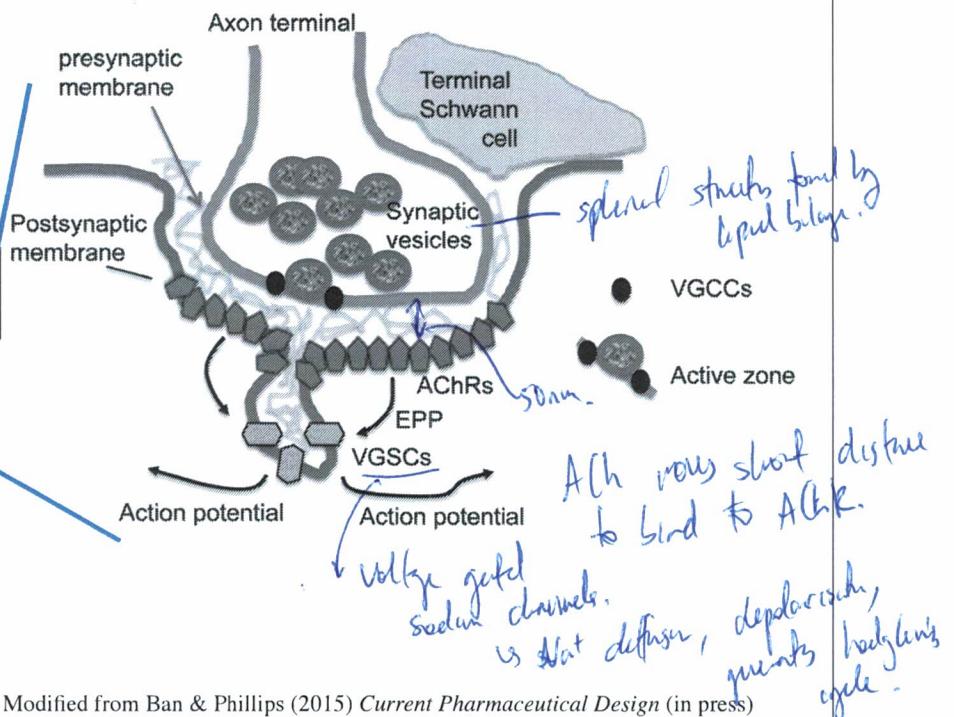
- Action potential depolarises nerve terminal
- *Voltage-gated  $\text{Ca}^{2+}$  channels (VGCCs)* in nerve terminal open, permitting influx of  $\text{Ca}^{2+}$
- $\uparrow [\text{Ca}^{2+}]_i$  in nerve terminal triggers *exocytosis* of *chemical neurotransmitter* (acetylcholine) into the synaptic cleft
- Acetylcholine binds and opens postsynaptic acetylcholine receptors (AChRs): *ligand-gated cation channels*
- *Inward  $\text{Na}^+$  current* depolarises the postsynaptic membrane: the *endplate potential (EPP)* (*depolarised potential*).  
↳ triggers action potential.
- EPP activates *voltage-gated  $\text{Na}^+$  channels (VGSCs)*

The nerve terminal branches of a single neuromuscular Synapse (plan view)





### Cross-section through a terminal branch



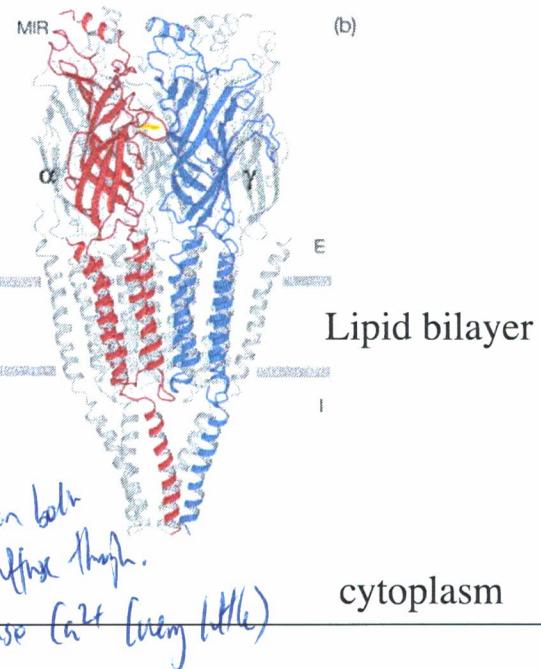
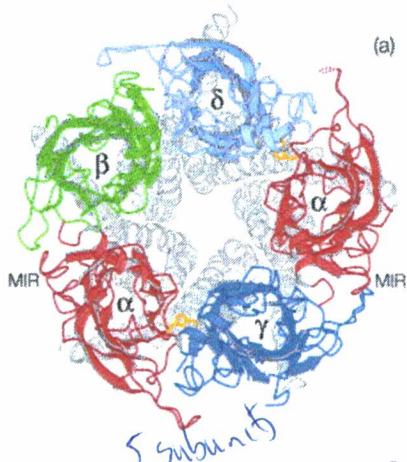
Modified from Ban & Phillips (2015) *Current Pharmaceutical Design* (in press)

### AChRs: example of a ligand-gated cation channel

View from the  
Synaptic cleft

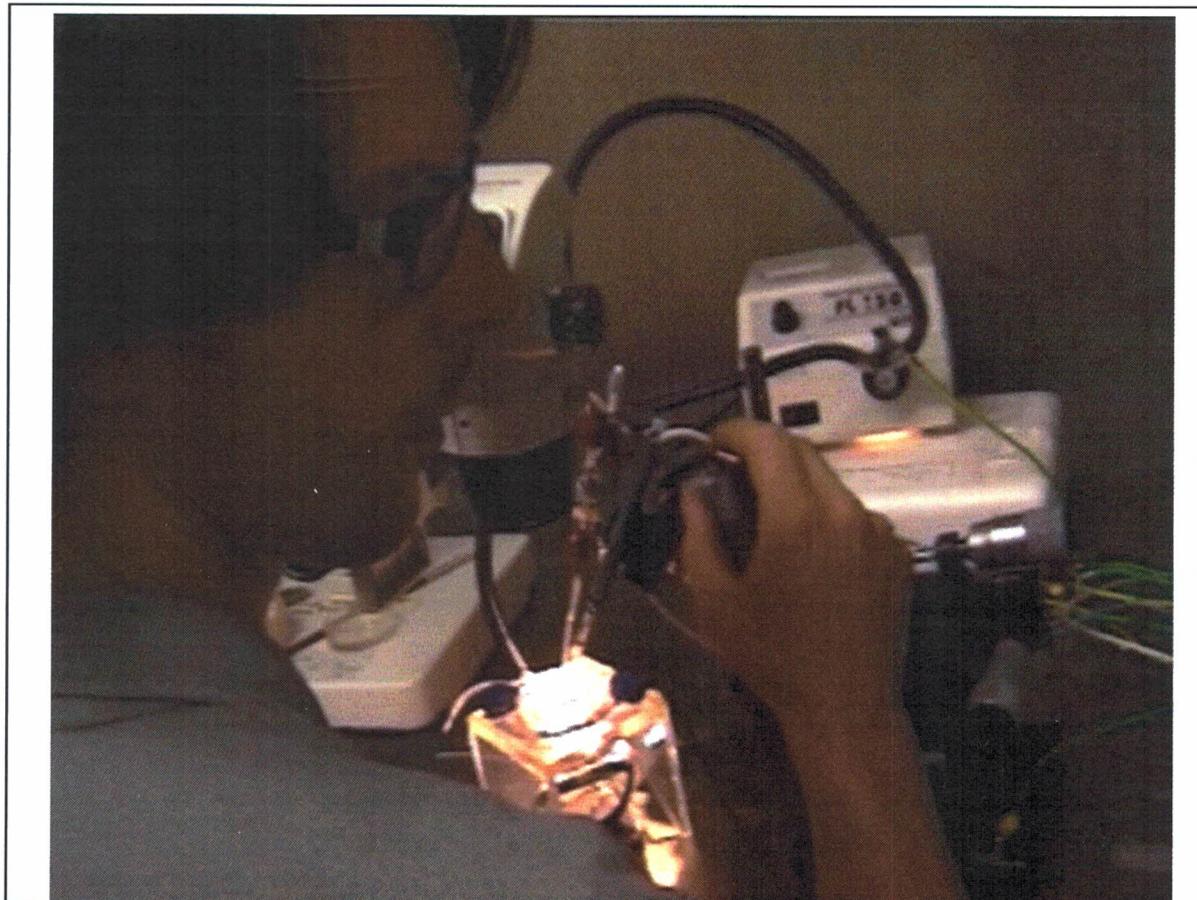
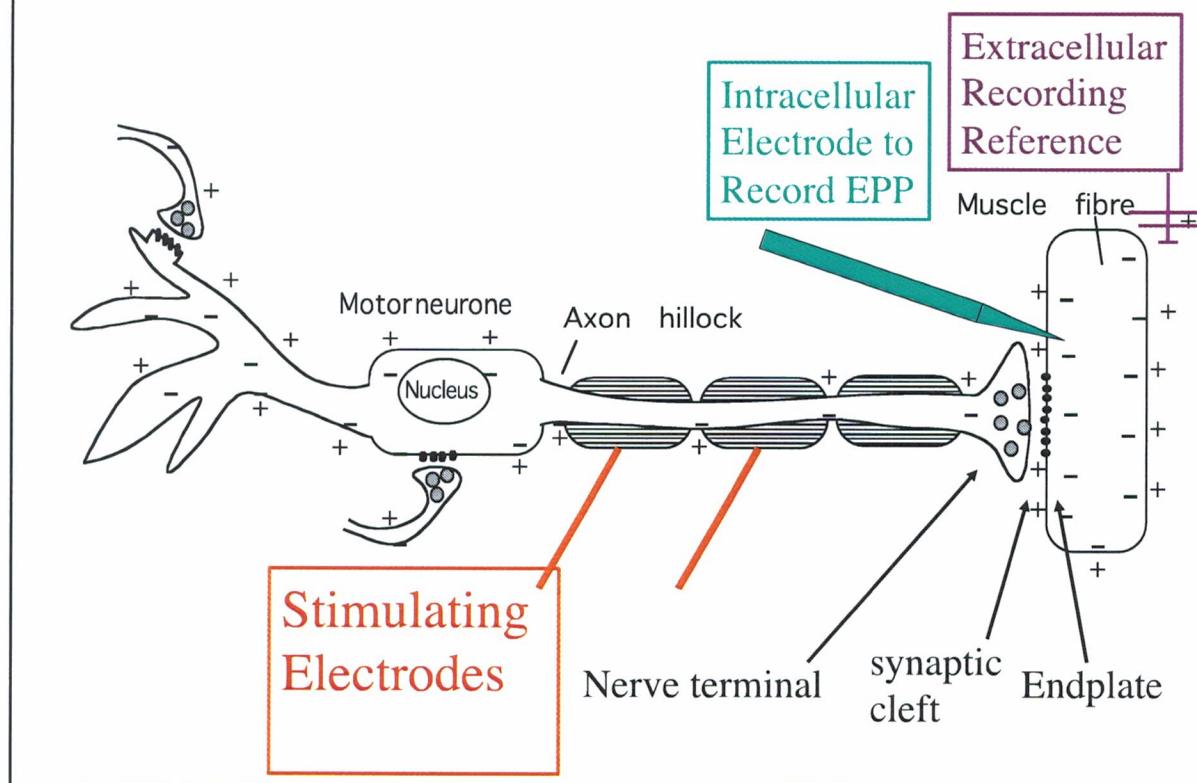
View from the  
side

Extracellular

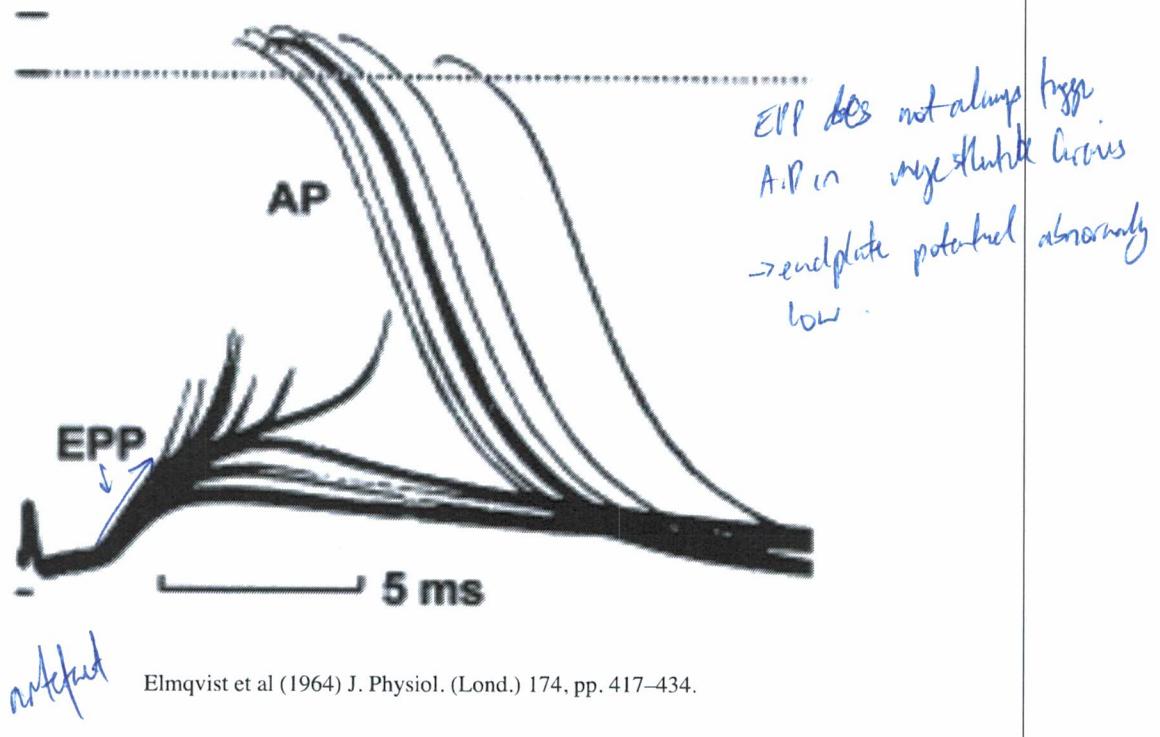


Unwin, N. (2005) *J Mol Biol.* 346, 967-989.

## Recording Postsynaptic potentials (e.g. the EPP)



## Relationship between EPP and muscle action potential



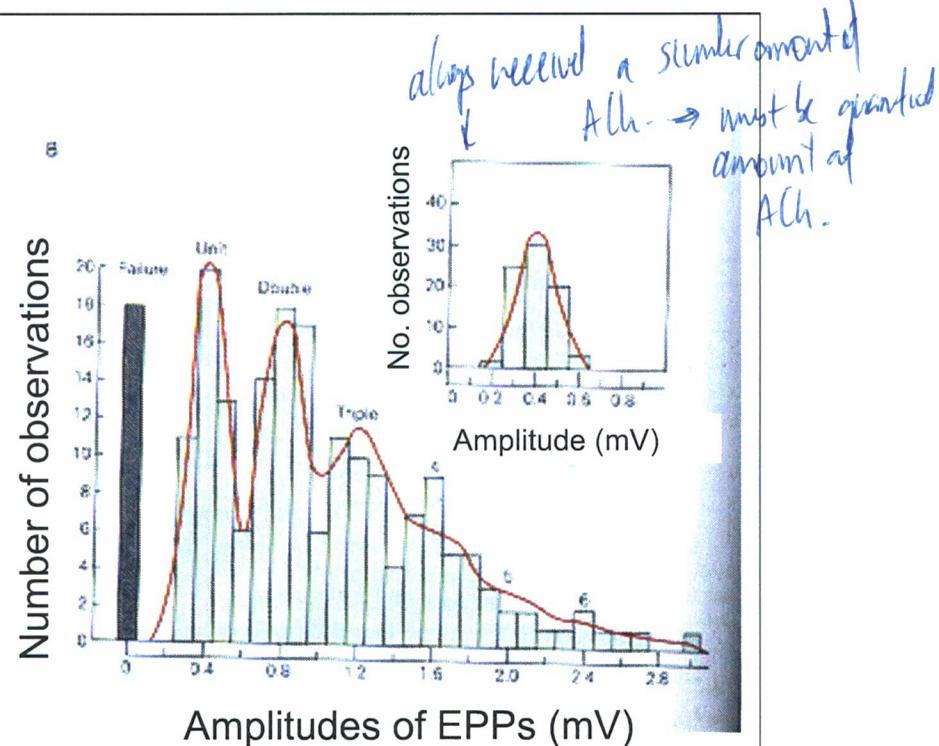
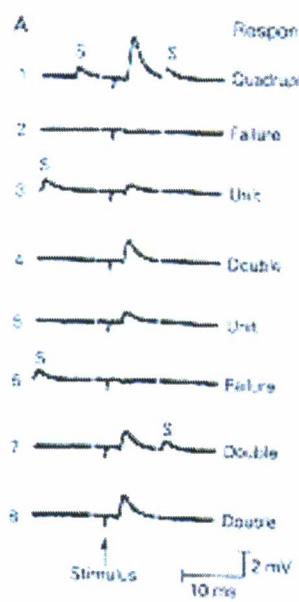
### Evoked *Endplate potentials* (EPPs) and spontaneous *miniature endplate potentials* (mEPPs)

- Each time the nerve is stimulated to evoke a nerve action potential a few milliseconds later we can record a brief depolarisation (amplitude  $\sim 20\text{mV}$ ) from our electrode in the muscle fibre called the **Endplate Potential (EPP)**
- Even when there are no action potentials in the nerve we can still record occasional depolarisations, smaller in amplitude than EPPs ( $\sim 0.5\text{mV}$ ), called spontaneous **miniature endplate potentials (mEPPs)**

## Amplitude of EPP depends on $[Ca^{2+}]_o$

- $[Ca^{2+}]_o$  normally  $\sim 1\text{mM}$ .
- If  $[Ca^{2+}]_o$  is lowered the amplitude of the EPP falls greatly from  $\sim 20\text{mV}$  to as little as  $0.5\text{mV}$
- At low  $[Ca^{2+}]_o$  EPP, becomes small & unreliable:  
Sometimes no EPP, sometimes  $0.5\text{mV}$  sometimes  $1.0\text{mV}$  sometimes  $1.5\text{mV}$ , occasionally  $2.0\text{mV}$ , suggesting that ACh is released in quanta

Recordings/traces

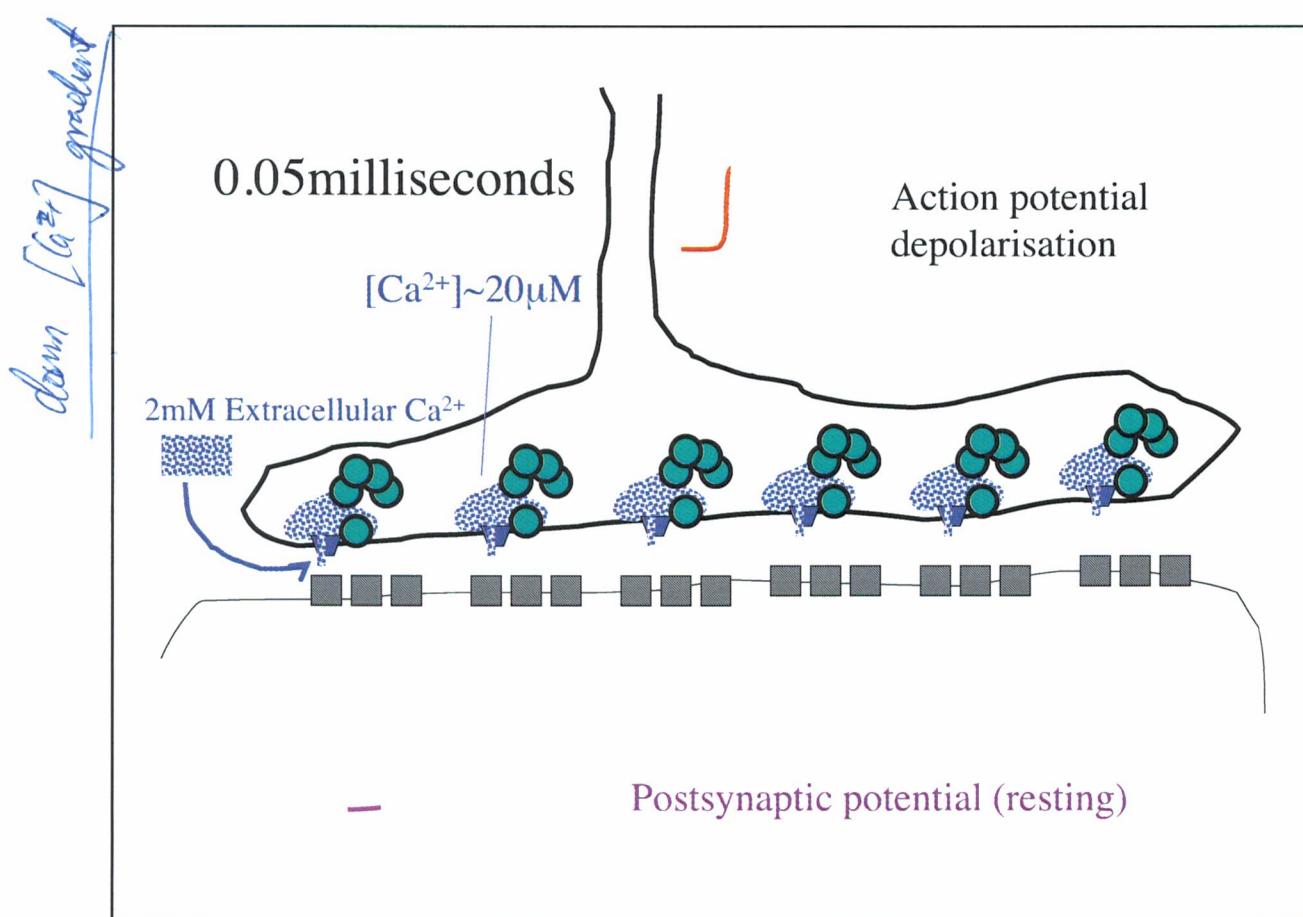
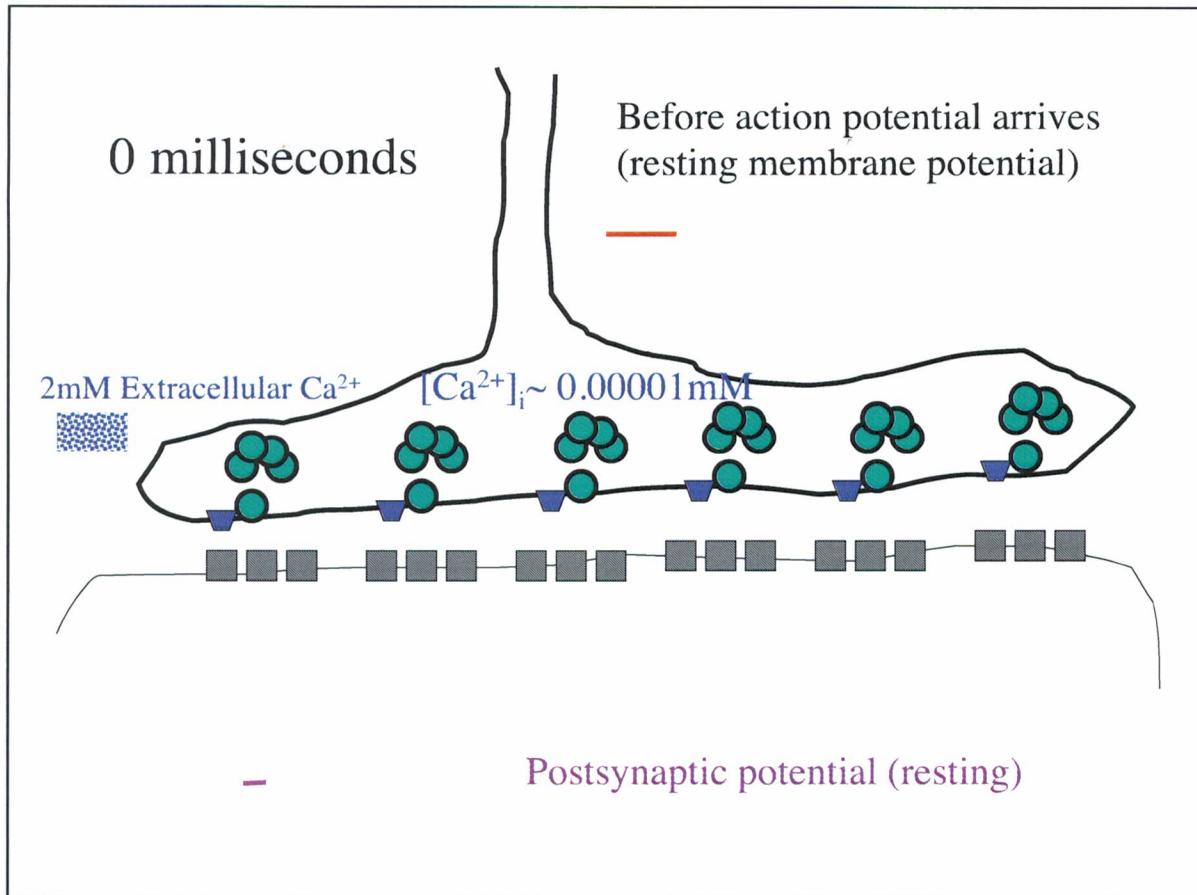


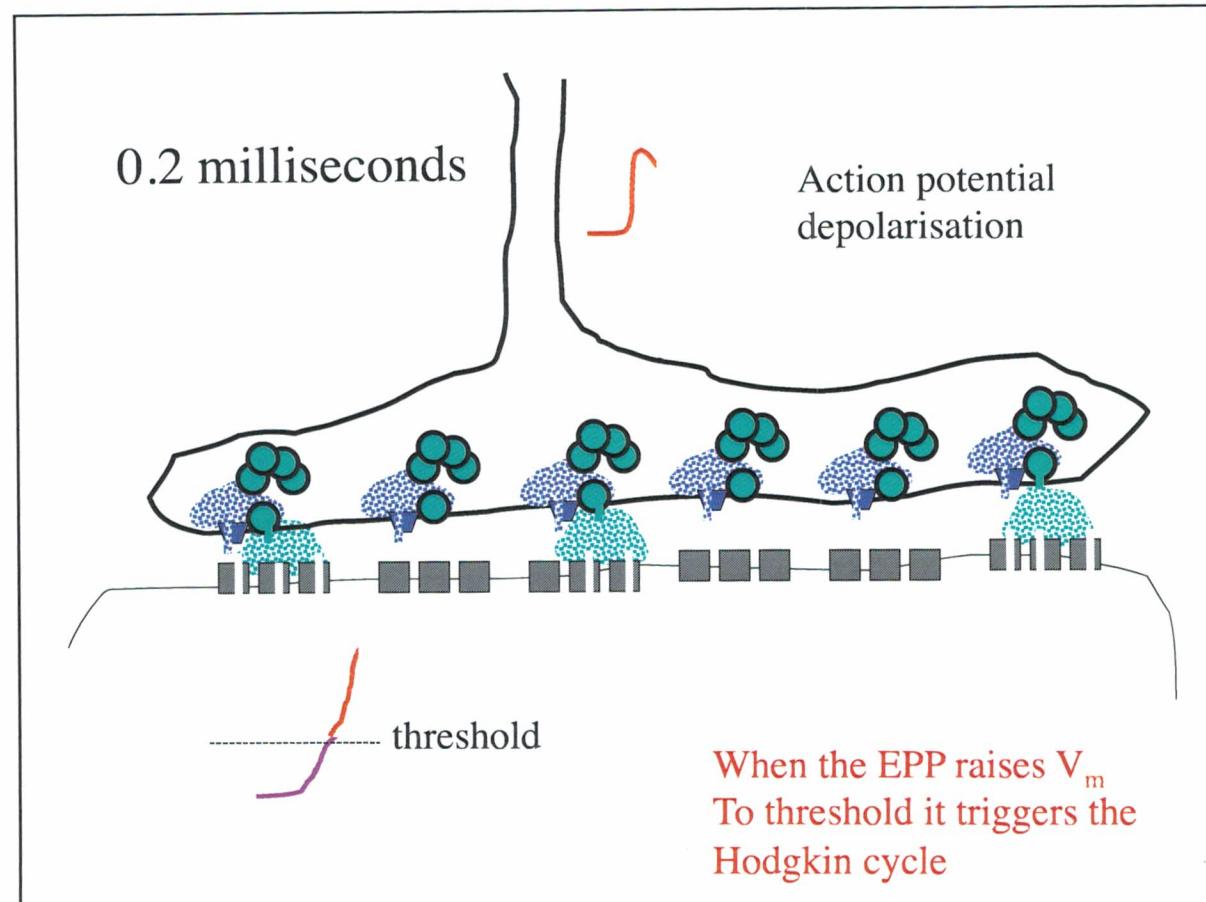
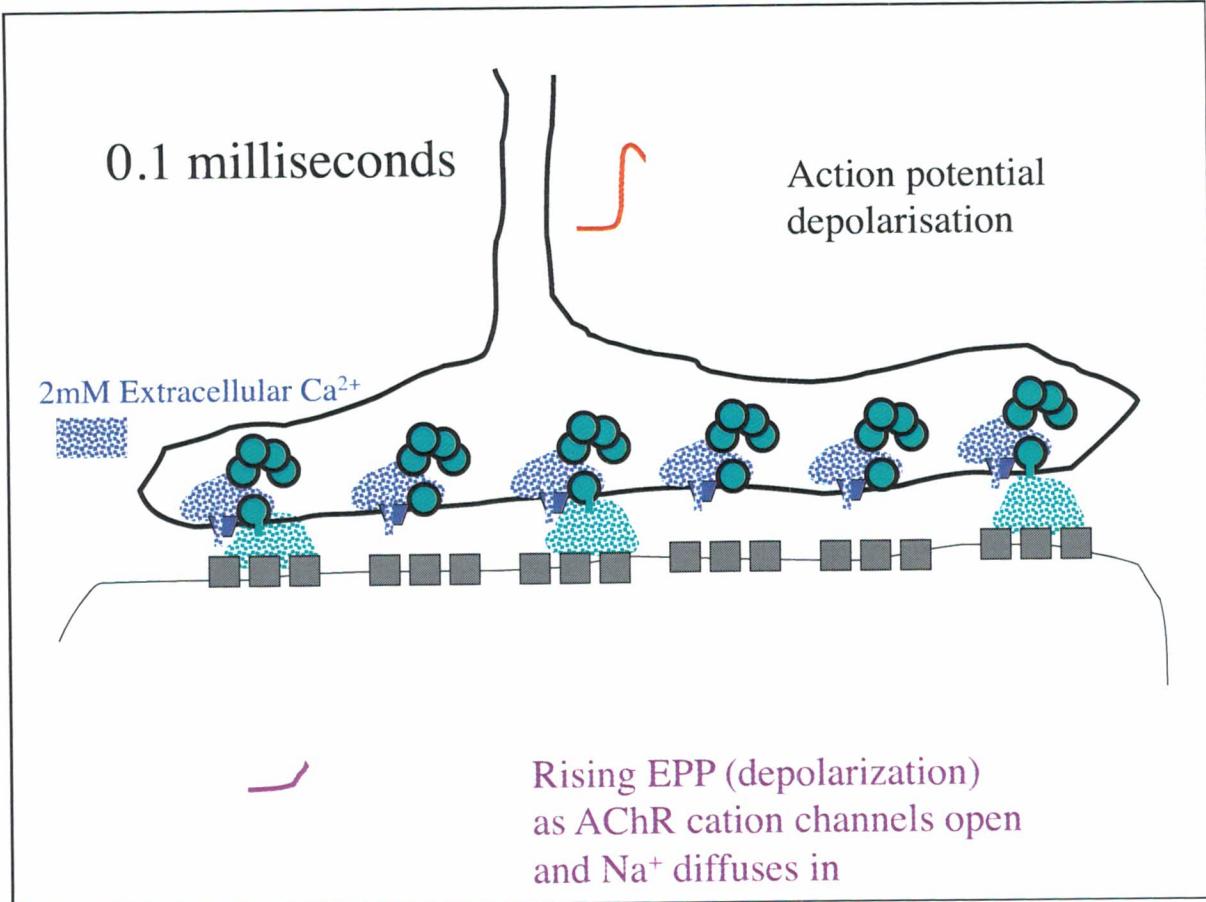
# Quantal synaptic transmission

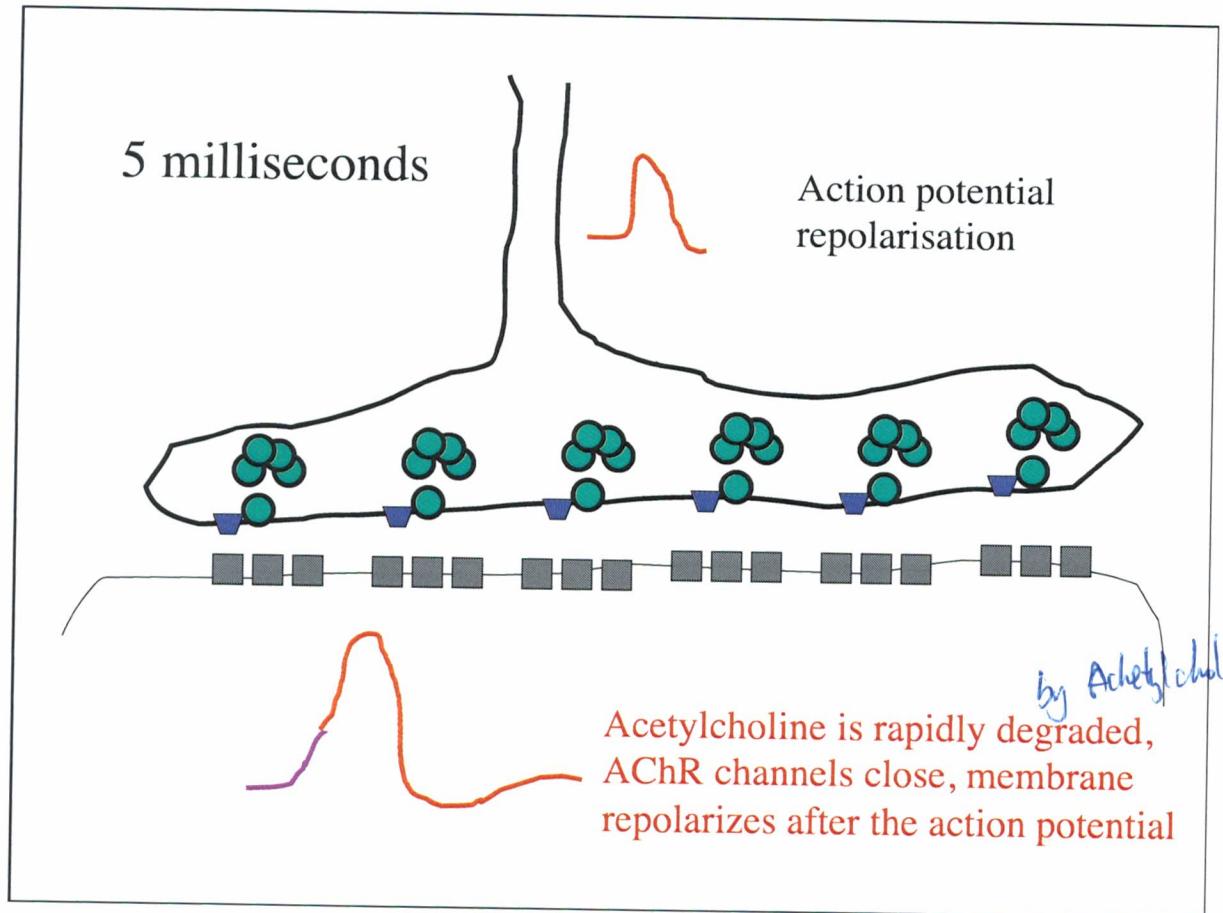
- The consistent size of mEPPs suggests that acetylcholine is released from the nerve terminal in discrete packets (quanta)
- The amplitude of the EPP depends upon the extracellular concentration of calcium
- At low extracellular calcium concentrations the amplitude of the EPP is a multiple of the amplitude of the mEPP, suggesting that the EPP is the sum of quanta, released in a *calcium-dependent, probabilistic*, manner

## Contents of a synaptic vesicle is the quantum

- The vesicle hypothesis says that these quanta of neurotransmitter are contained in membrane-bound *synaptic vesicles* that are released by regulated *exocytosis*  
*filled by Ca<sup>2+</sup>*  
*more release.*  
*discarded*  
*Vall.*
- Exocytosis of quanta thought to be triggered in a probabilistic way when calcium enters the nerve terminal
- The uniform diameter of the synaptic vesicles and uniform filling of each vesicle by *pumps* in the vesicle membrane may explain the fairly consistent *quantal amplitude* of the postsynaptic response.







*number of synaptic vesicles*

Quantal content depends upon how much calcium enters the nerve terminal after the nerve terminal depolarizes.

Quiz questions:

Q1. How would the quantal content be altered if the extracellular concentration of calcium was to be reduced from 2mM to 1mM?

INCREASE?      DECREASE?

*reduce concentration gradient,  
less  $\text{Ca}^{2+}$  enters the cell.*

Q2. Why would a reduction in extracellular calcium concentration cause such a change in quantal content?

### Quiz question:

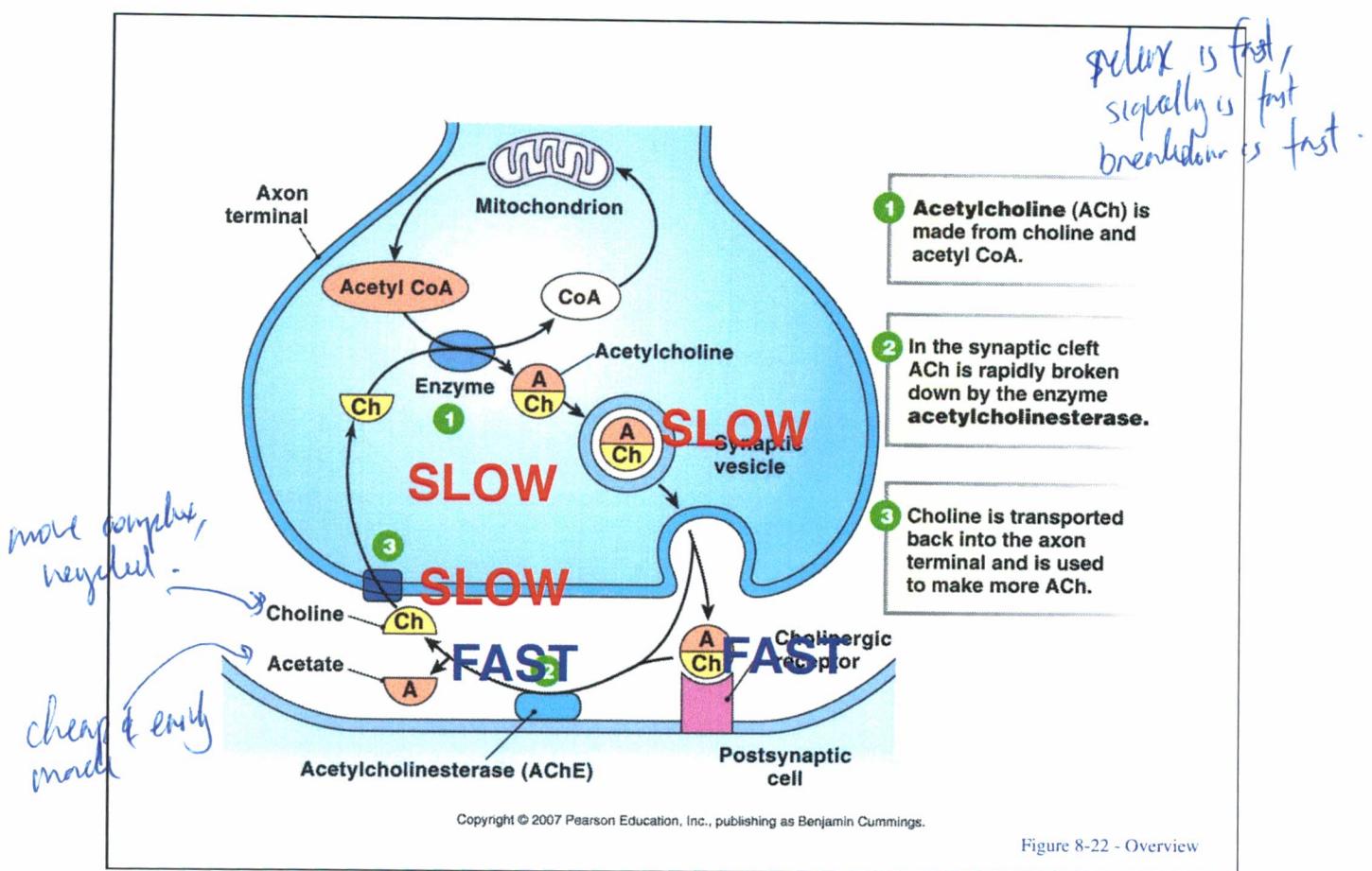
Q3. How would an increase in quantal content alter the amplitude of the EPP?

INCREASE?

DECREASE?

# Recycling and recovery after neuromuscular transmission

- Neuromuscular transmission occurs in bursts of activity
- Acetylcholine must be removed from the synaptic cleft to terminate the EPP
- Choline must be recycled
- Synaptic vesicles must be recharged and prepared for another round of neuromuscular transmission



## Learning objectives: Synaptic transmission

- P4.1 What are meant by the "presynaptic" and "postsynaptic" parts of the synapse? What are their respective roles?
- P4.2 List the sequence of events in neuromuscular synaptic transmission: from the nerve action potential till the muscle action potential.
- P4.3 Draw a cross-section through a neuromuscular synapse, labelling the location of voltage-gated  $\text{Ca}^{2+}$  channels, synaptic vesicles, acetylcholine, nicotinic acetylcholine receptors, acetylcholinesterase and voltage-gated  $\text{Na}^+$  channels.
- P4.4 Describe the function of each of these components in the process of synaptic transmission.

## Learning objectives: Synaptic transmission

- P4.5 Describe three features that make the *nicotinic acetylcholine receptor* an example of a *ligand-gated cation channel*.
- P4.6 What are *synaptic vesicles* and how are they affected by calcium influx into the nerve terminal?
- P4.6 What is the *endplate potential* (EPP) and how is it recorded?
- P4.7 What is a *spontaneous miniature endplate potential* (mEPP) and what phenomenon is it thought to represent?
- 4.8 What is meant by "*the probabilistic nature of transmitter release*" and why do changes in the extracellular concentration of  $\text{Ca}^{2+}$  influence it?

## Learning objectives: Synaptic transmission

P4.9 What are meant by *quantal amplitude* and *quantal content*. What factors influence each of these parameters at the NMJ?

P4.10 What is the relationship between the endplate potential amplitude, quantal amplitude and quantal content?

P4.11 If the concentration of calcium ions in the extracellular fluid ( $[Ca^{2+}]_o$ ) was raised from 0.5mM to 2mM, in what way would this effect synaptic transmission? What is the mechanism?

## Learning objectives: Synaptic transmission

P4.12 What terminates the action of acetylcholine on the acetylcholine receptors? How does it do so?

P4.13 Describe the processes by which acetylcholine is recycled at the neuromuscular junction and why this recycling is important.

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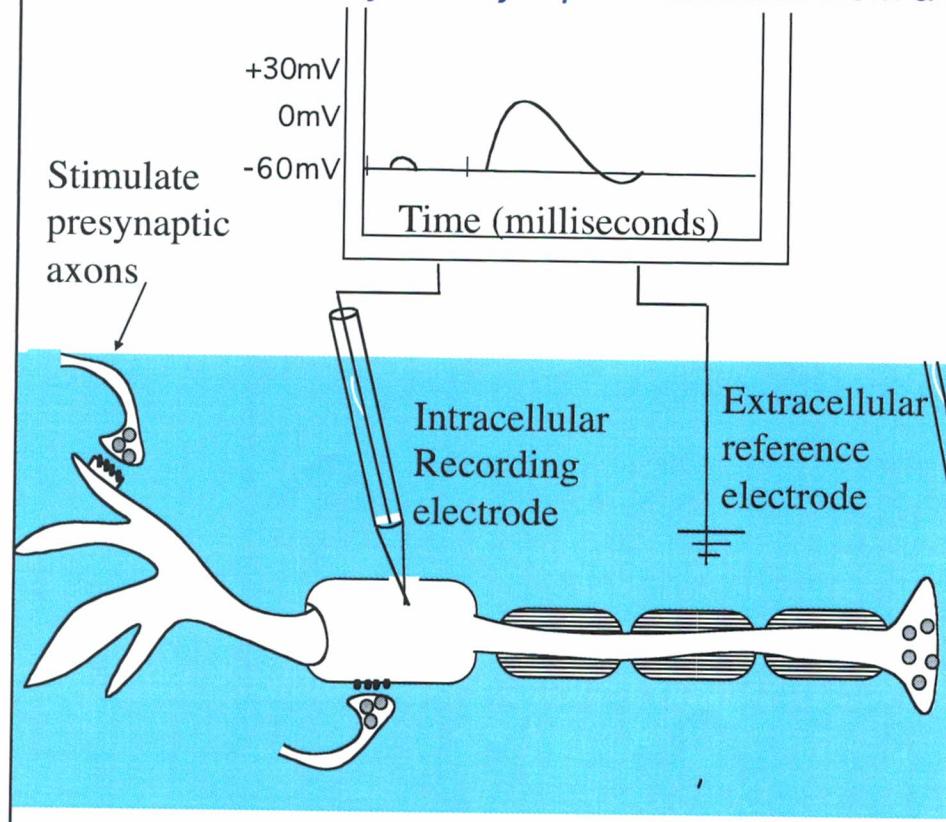
PHSI2005/2905 Cellular Neurophysiology Lect. 5 - Dr Bill Phillips

## Central nervous system transmission

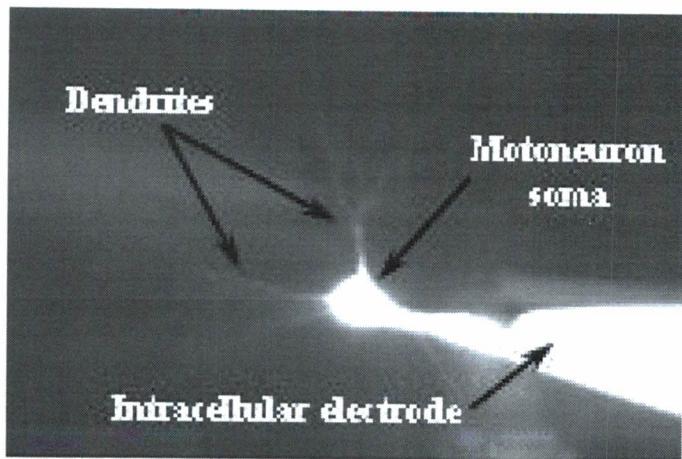
10/04/15

- *Fast glutamateric synapses* on neurons: similarities and differences from the NMJ
- *Fast inhibitory synapses* on neurons
- Inhibitory chloride channels moderate the effect of depolarising currents upon depolarisation of the soma
- Summation of *postsynaptic currents* in neurons: cable properties revisited
- Diversity of neurotransmitters and their postsynaptic receptors
- *Neuromodulation*: producing changes in neuron excitability

### Record Excitatory Postsynaptic Potentials from a motor neuron



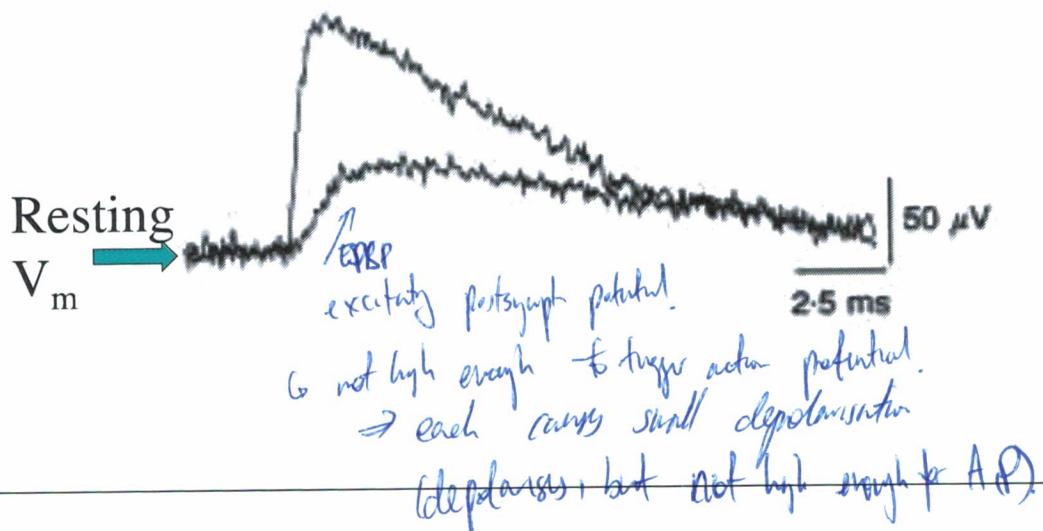
Intracellular recordings from the soma of a motor neuron



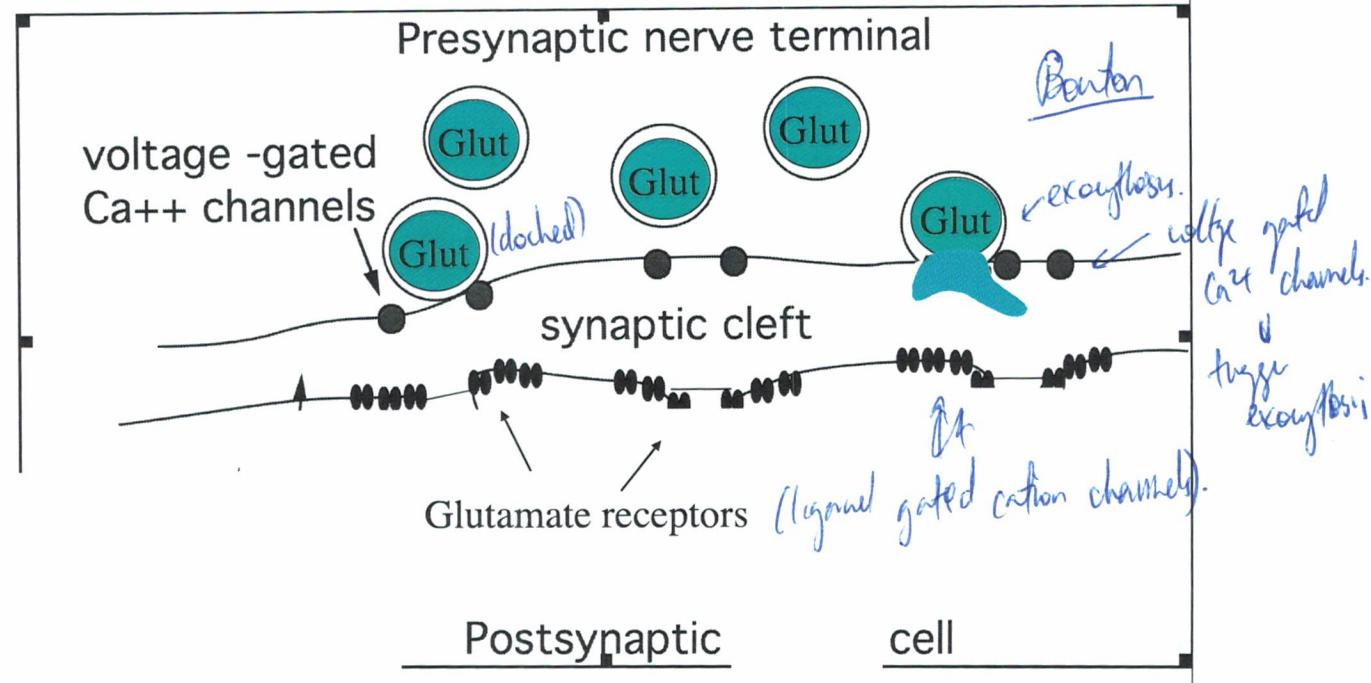
## Excitatory Postsynaptic Potentials (EPSP)

stimulate stretch receptor  
afferent nerves

### Sub-threshold EPSPs in a motor neuron



Neurotransmitter release mechanism similar to the neuromuscular junction (but with glutamate as transmitter)



*Ligand-gated cation channels* like the nicotinic acetylcholine receptor (AChR) and many glutamate receptors are permeable to both  $\text{Na}^+$  and  $\text{K}^+$ .

Q. Why does opening of such cation channels result in depolarisation of the postsynaptic membrane?

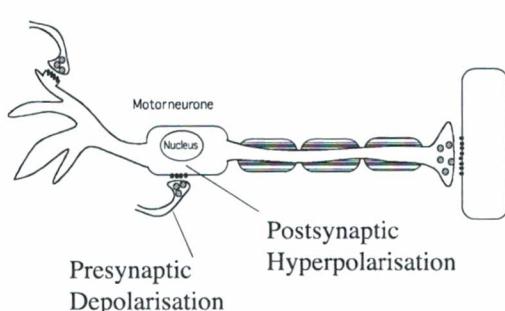
(Hint: consider the Nernst Potentials for  $\text{Na}^+$  and  $\text{K}^+$ )  
membrane due to N.P for  $\text{K}^+$  than N.P for  $\text{Na}^+$ , <sup>not</sup> resting potential.  
 $\therefore$  smaller driving force of  $\text{K}^+$  than on  $\text{Na}^+$ .

## Different synapses in the brain use diverse neurotransmitters

- ACh - muscle excitation . (NAChR)
  - Glutamate (excitatory)
  - Glycine
  - Gammaaminobutyric acid (GABA) ] inhibition.
  - Serotonin/5-hydroxytryptamine (5-HT)
  - Dopamine
  - Noradrenaline/norepinephrine
  - ATP
  - Etc.
- } own specific notes -

# Neurotransmitters can act via multiple different receptors

- Acetylcholine
- Glutamate
- GABA
- ATP
- Nicotinic (several) and muscarinic
  - AMPA, NMDA, metabotropic types (multiple of each)
  - $\text{GABA}_A$  (multiple),  $\text{GABA}_B$ ,  $\text{GABA}_C$
  - P2X(1-7), P2Y (several)



\*Often found on neuron soma and proximal dendrites

(drawn in 19(18)  
fasts prewh inhibitory  
synapses.)

Major inhibitory neurotransmitters:  
Gamma amino butyric acid (GABA), glycine

Acting via: Ligand-gated  $\text{Cl}^-$  channels (e.g.  $\text{GABA}_A$  receptor, glycine receptor)

hyperpolarise by activating ligand gated  $\text{Cl}^-$  channels,

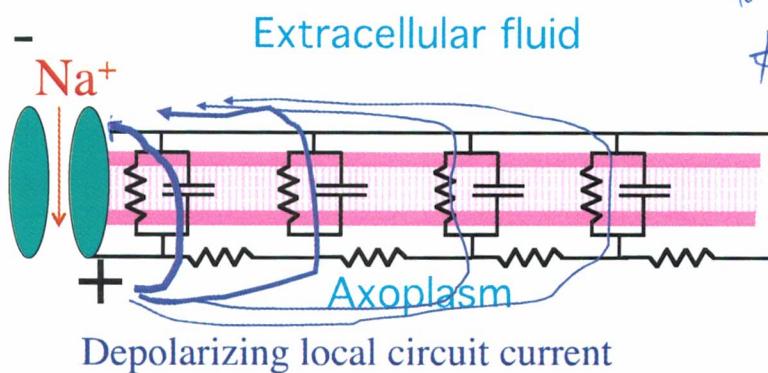
$[\text{Cl}^-]_o > [\text{Cl}^-]_i$ ,  
 $\therefore \text{Cl}^-$  moves in, more  $-V_L$ .

## Ligand-gated chloride channels

- GABA<sub>A</sub> receptors and glycine receptors are examples of ligand-gated channels selective for Cl<sup>-</sup> (GABA<sub>A</sub>, glycine being the respective ligands)
- [Cl<sup>-</sup>]<sub>o</sub> >> [Cl<sup>-</sup>]<sub>i</sub> concentration gradient into cell (inward chemical driving force)
- Opening of these channels tends to pull the membrane potential closer to the Nernst Potential for chloride (~ -70mV) and prevent depolarization.
- They can hyperpolarise the soma, or *shunt* depolarising local circuit currents coming from excitatory synapses

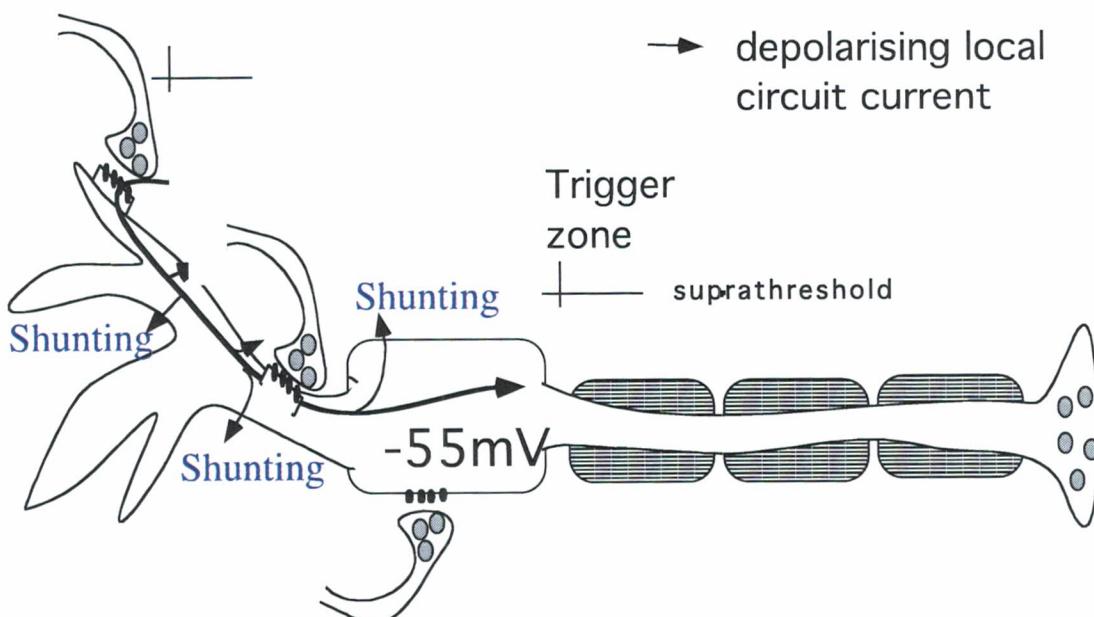
can make membrane potential even lower.

## What do I mean by *shunting*?

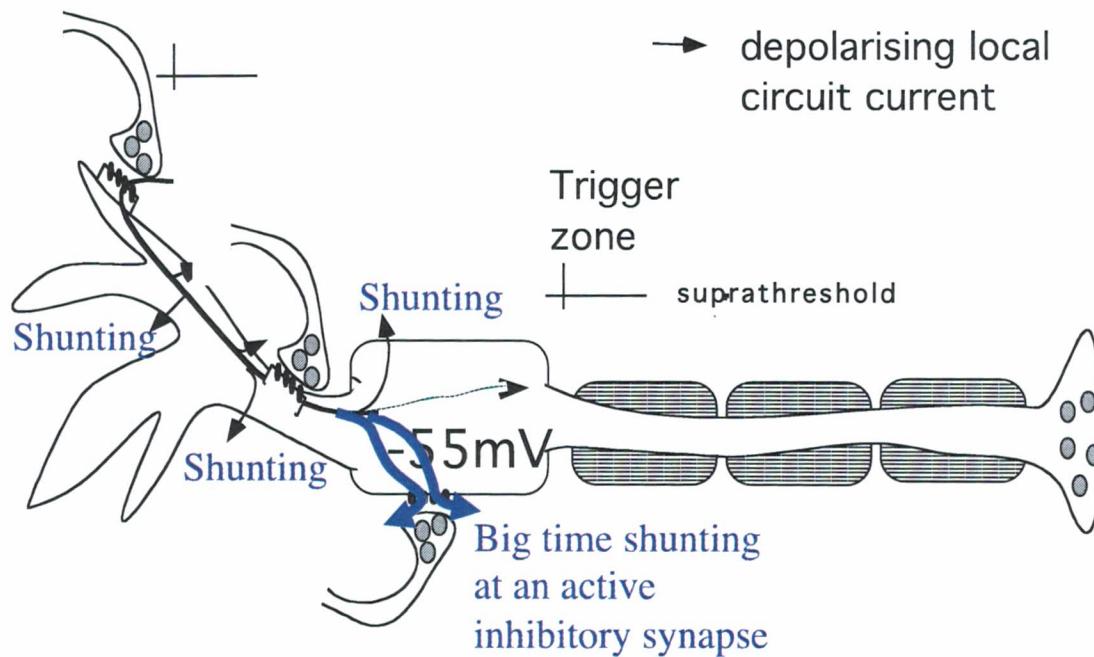


Previous example of shunting = short-circuiting of depolarizing local circuit current (in the axon). Current seeps out through leakage channels diminishing the currents it passes along the axon or dendrite from where the current was generated

Depolarising local circuit current generated at glutamatergic synapse on a dendrite



Opening of *ligand-gated Cl<sup>-</sup> channels* at inhibitory synapses increase the shunting of excitatory local circuits



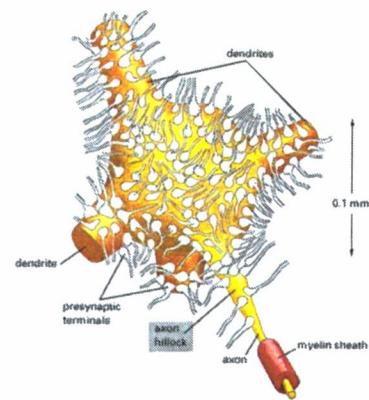
## Summation of postsynaptic currents

- Excitatory Postsynaptic Currents (EPSCs) spread through dendrites and sum together in the cell body (soma)
- Local circuit currents diminish with distance along the dendrites due to resistance of cytoplasm (like axoplasmic resistance) and shunting via leakage channels
- EPSCs from many synapses on different branches of the *dendritic tree* sum together at the axon hillock where a 'decision' is made whether an action potential/s is triggered

current diminish with distance  
↳ leakage  
↳ resistance

## Synaptic integration

- Plasma membrane stores electrical charge (capacitance properties) this means brief openings of channels cause prolonged changes in  $V_m$

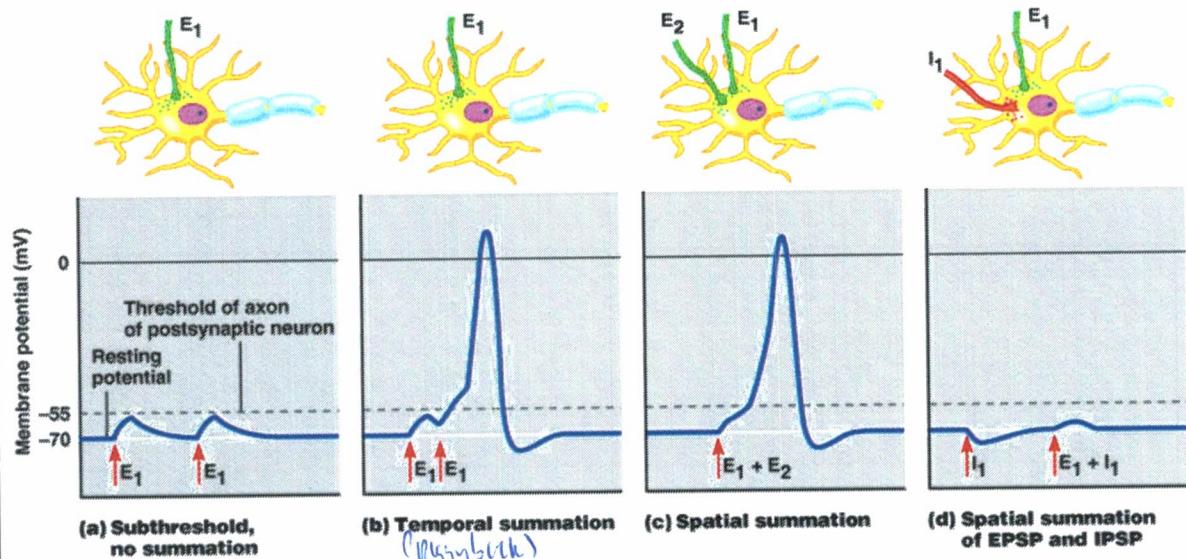


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- Brief *Excitatory Postsynaptic Currents* (EPSCs) that occur a few milliseconds apart therefore *summate* to raise  $V_m$
- When *Inhibitory Postsynaptic Currents* (IPSCs) occur at the same time as EPSCs they help to hold down the  $V_m$  near  $E_{Cl}$ , thereby reducing the chance that action potentials will be triggered at the axon hillock

takes a while to depolarize (reduce charge & resty (un))  
↳ multiply can add & propagate

receptor GABA or glycine, pushes  $V_m$  to  $E_{Cl}$  ( $\approx -70 \text{ mV}$ )



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Fig 11.21 From Human Anatomy & Physiology by Marieb, E.N. 6th Edn

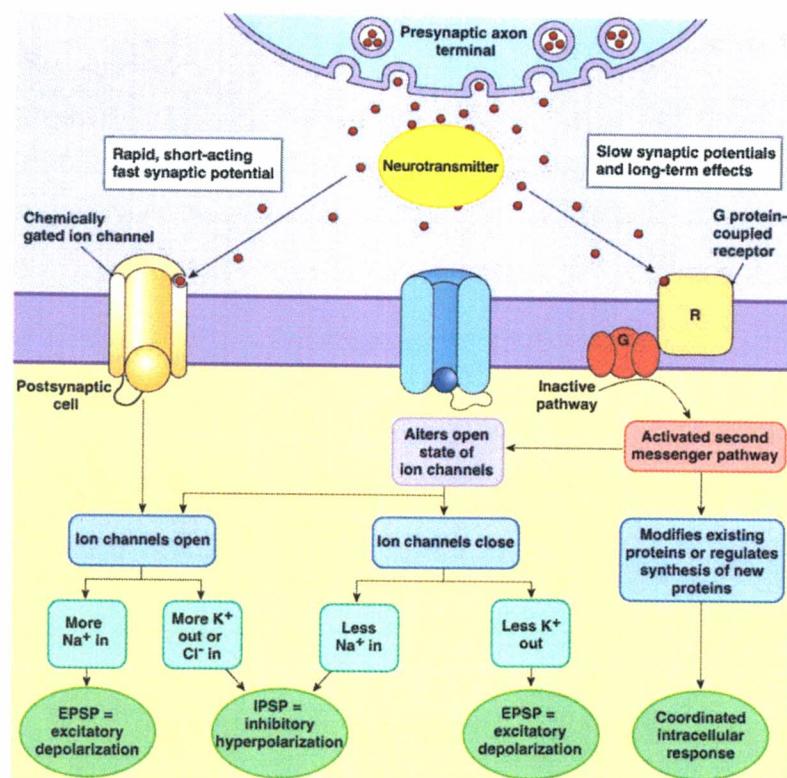
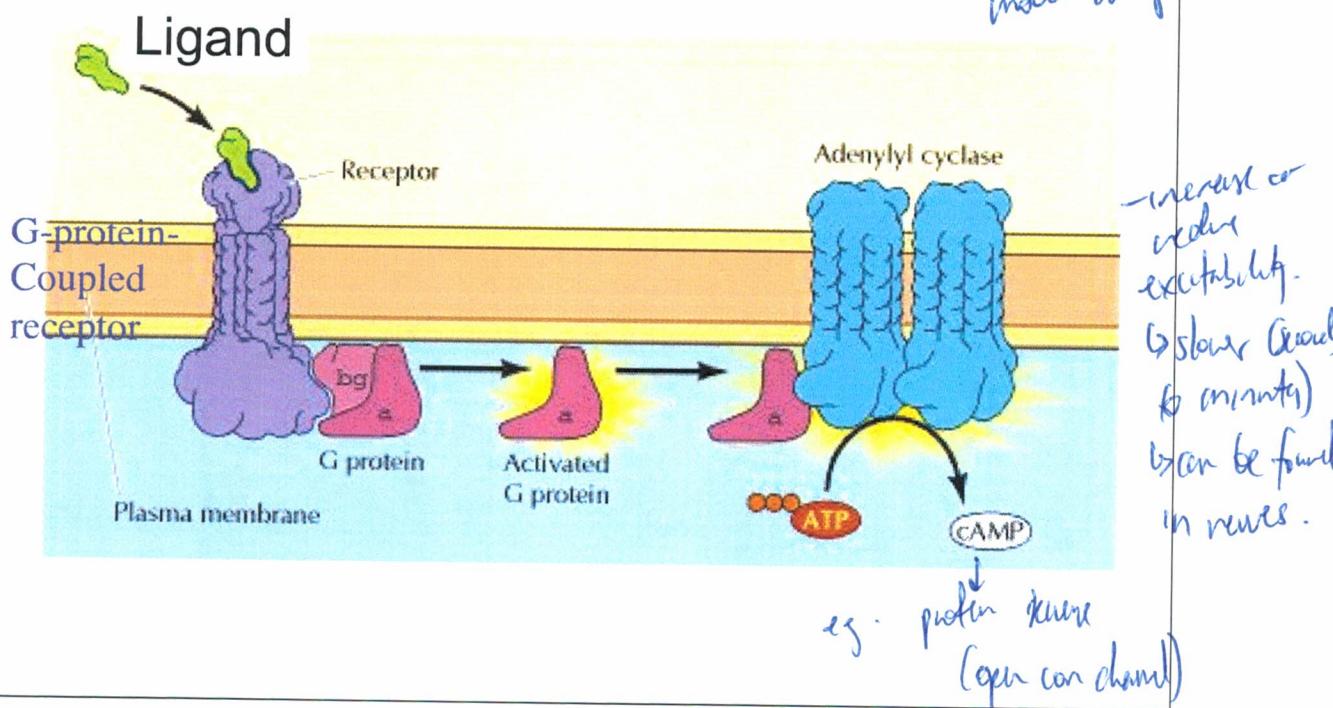
## Neuromodulators

receptors activated by Glu / GABA -  
G-protein coupled receptors (2ndary receptor)

- Apart from ligand-gated ion channels, neurotransmitters and other ligands can also act via receptors that generate intracellular second messengers (e.g. cyclic AMP,  $\text{Ca}^{2+}$ ).
- Ligands that act via second messenger receptors are called *neuromodulators*
- G-protein coupled receptors and receptor tyrosine kinases are often involved in neuromodulation.
- Second messengers can cause longer term changes: either increasing or decreasing neuron excitability (for hundreds of milliseconds or even seconds)
- Neuron excitability can be reduced by a second-messenger activated  $\text{K}^+$  channels in the neuron membrane: the neuron is then less likely to fire action potentials

## Example of a second messenger: Cyclic AMP (cAMP)

can be responsible for mood changes.



## Second messenger pathways can modify 'excitability' of neurons by:

- Modifying ligand-gated ion channels at synapses so they are more (or less) effective as ion channels
- Increasing or decreasing the function of certain K<sup>+</sup> channels so that EPSCs are more (or less) effective at raising the V<sub>m</sub>
- Acting *presynaptically* on the nerve terminal to increase (or decrease) the amount of transmitter released per pre-synaptic action potential

## Learning objectives: CNS transmission

P5.1 What are the similarities in structure and function between the neuromuscular junction and the fast, *glutamatergic* synapses on the dendrites of the motor neuron? Identify three differences.

P5.2 In what respects are fast *glycinergic* and *GABAergic* synapses similar to glutamatergic synapses and in what ways are they different? Refer to the driving forces and charges for the particular ions involved.

P5.3 With the aid of a drawing, explain the way in which depolarising inward currents at synapses on the dendrites of a motor neuron can depolarize the cell soma (body) and axon hillock.

## Learning objectives: CNS transmission

P5.4 Describe the influence of *glycinergic* and *GABAergic* synaptic activity upon the excitability of the motor neuron.

P5.5 Using a drawing of a motor neuron, explain how chloride channels at inhibitory synapses moderate the depolarising currents during EPSPs.

P5.6 Outline ways in which different neurotransmitters and multiple receptor types can work together to shape the firing activity of a neuron.

P5.7 In what sorts of ways can *neuromodulators* act on cells? What is meant by the term *second messenger*, and how can they influence neuron excitability?

## Getting on top of this series of lectures

If you are having difficulty writing a convincing short answer response (2-3 sentences) to any of the learning objectives from my five lectures then:

1. Read the supplementary notes downloadable from:  
<http://www.physiol.usyd.edu.au/~billp/neurosppnotes.wdp.pdf>
2. Look up the terms/phrases you do not understand in a text book or by online search
3. Mark the subset of learning objectives you still can't understand and forward them to Bill Phillips  
<william.phillips@sydney.edu.au> to be considered in the Review lecture session. First, in best dressed.

## SUPPLEMENTARY NOTES FOR CELLULAR NEUROPHYSIOLOGY

PHSI2005 & 2905 – Semester 1, 2012

A/Prof. Bill Phillips, Discipline of Physiology, University of Sydney

### **Electrical potentials and the electrochemical equilibrium across the cell membrane**

Signalling by neurons involves changes in the electrical potentials across their membranes

Signalling by neurons in the nervous system has long been known to involve electrical potentials (voltage differences) which could be measured, for example, by placing electrodes on the surface of the skull (EEG). When physiologists developed techniques for placing tiny electrodes inside neurons (in the 1940s and 50s) they were able to measure **electrical potential differences** across the plasma membrane of the cell and to show that signalling by neurons involved transient changes in the value of this **membrane potential**. In a healthy neuron that is not in the process of signalling (resting), the inside of the cell (the cytoplasm) is more negative than the outside of the cell (extracellular) and this **resting membrane potential** is thus about -65 millivolts (mV) or -0.065 volts. All types of healthy cells have a membrane potential.

### The lipid membrane of the neuron separates different concentrations of ions

The plasma membrane consists of a **lipid bilayer**. The phospholipids that make up this bilayer have one hydrophilic end (a charged or polar group such as a phosphate group) and a hydrophobic (uncharged, non-polar) tail. Lipids of this type tend to spontaneously form into a **lipid bilayer** which is a lower energy state for them because the **hydrophobic tails** can interact with each other and the **hydrophilic head groups** can interact with water molecules (which are highly polar) on either side. Large numbers of **intrinsic (integral) membrane proteins** float within the lipid bilayer. They span the bilayer with their hydrophobic amino acid residues spanning the hydrophobic core of the membrane. Molecules or ions that are charged or polar (such as ions) cannot easily pass through the bilayer because of its hydrophobic centre.

To try to explain the electrical potential across the membrane physiologists examined the concentrations of ions on either side of the membrane. They found that inside the plasma membrane the concentrations of **potassium ions ( $K^+$ )** and **organic anions ( $A^-$ )** were much higher than in the extracellular fluid while the concentrations of **sodium ions ( $Na^+$ )** and **chloride ions ( $Cl^-$ )** were much lower than outside. These are the types of ions that are most important in signalling along neurons.

Typical distribution of major ions across the neuron membrane (Pearson)

<b>Ion</b>	<b>Cytoplasm (intracellular fluid) (mM)</b>	<b>Extracellular Fluid/plasma (mM)</b>	<b>Nernst potential*</b> (mV)
$K^+$	150	5 (normal range 3.5-5)	-90
$Na^+$	15	145 (normal range 135-145)	+60
$Cl^-$	10 (5-15)	108 (normal range 100-108)	-63
$Ca^{2+}$	1	0.0001	

\*Meaning membrane potential at which there is no net movement of the ion in question across the membrane calculated for 37°C. Note that every cell will differ slightly in its intracellular concentrations and the associated Nernst Potentials. Extracellular fluid/plasma concentrations can vary beyond the ranges in sickness.

### **Electrochemical equilibrium**

There are **two forces working on every ion**. The first is a chemical force due to the **concentration gradient**; energy is required to concentrate substances and where a concentration gradient exists, ions, like non-charged molecules, will diffuse down the gradient towards the region of lower concentration (i.e. there is a 'chemical' force wanting to move them across the membrane: sodium into the cell, potassium out of the

cell etc.). The second force acting on every ion is the **electrostatic force** due to its electrical charge.

Pore-forming proteins in the neuron membrane selectively allow particular types of ions to pass through

The forces acting on ions would have no effect if ions couldn't pass through the membrane, but sodium, potassium and chloride ions can move across the membrane through pores in the membrane. These pores are formed by **ion channel proteins**. The structure of these ion channels is such that they are selective for particular types of ions according to the size, shape and charge properties the ions. The negatively charged organic ions ( $A^-$ ; these include negatively charged cytoplasmic proteins and molecules such as ATP) cannot pass through the membrane at all, meaning that there is a permanent concentration gradient of  $A^-$  across the membrane. On the other hand the neuron membrane is believed to contain ion channels selective for the positively charged ions (cations),  $Na^+$  and  $K^+$  and others selective for the negatively charged ion (anion),  $Cl^-$ , that are open all the time allowing each of these ions to move in or out of the membrane according to the forces working on them.

#### Electrochemical equilibrium for potassium ions

It is easiest to understand how membrane potentials are generated by considering the forces working on each ion one at a time. The electrostatic force can work for or against the concentration gradient of the ion in question. For example  $K^+$  is more concentrated inside the cell than outside, so the primary chemical force will attempt to move  $K^+$  through membrane channels and out of the cell but at the membrane potential of the resting neuron (about -65mV) the ion must work against the attraction of the net negative charge inside the cell and the repulsion due to the net positive charge outside the cell. If there was only  $K^+$  across the membrane to consider, then  $K^+$  would flow out of the cell and the shift of charge out of the cell would increase the opposing electrical driving force. Finally, the inward electrical driving force would exactly equal the outward chemical force due to the concentration gradient and there would be no net force on the  $K^+$  ion and thus no net movement (or flux). This situation is illustrated in Fig 1 below. The membrane potential at which this equilibrium occurs is called the **Nernst potential** for potassium ( $E_K$ ).  $E_K$  is typically about -75mV.

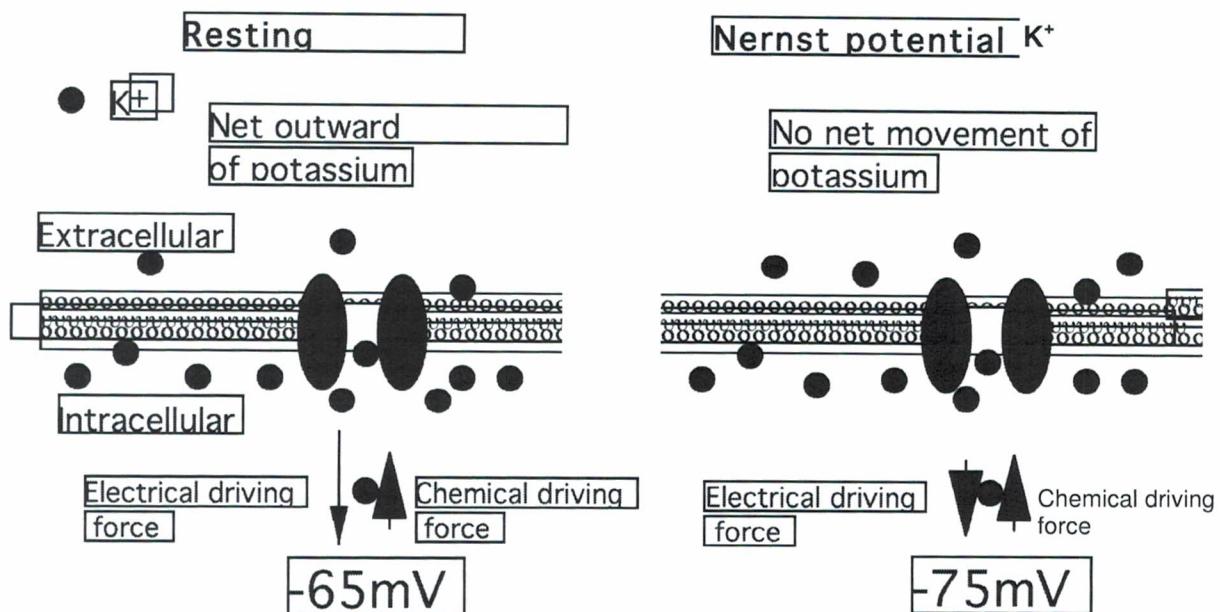


Fig 1.

Each of the ions that are distributed in a gradient across the membrane has its own Nernst potential (see table) and the Nernst potential can be calculated according to the formula (stated here for the case of potassium):

$$E_K = \frac{RT}{zF} \ln \frac{[K^+]_o}{[K^+]_i}$$

### Nernst equation for K<sup>+</sup>

Where  $E_K$  is the value of membrane potential for which K<sup>+</sup> is in equilibrium (**the K<sup>+</sup> Nernst potential**), R is the gas constant, T is temperature in degrees Kelvin, z is the valance of the ion (in the case of potassium it is +1), and F is the Faraday constant. The remainder of the equation is the natural logarithm (base e) of the ratio of [K<sup>+</sup>]<sub>o</sub> over [K<sup>+</sup>]<sub>i</sub> (the concentrations of K<sup>+</sup> on the outside and inside of the cell respectively).

[It is important to note though that the ion gradients do not run down during the functioning of healthy neurons as the rate of ion flow is small compared to the concentration differences and there are transporter proteins (pumps) that work to maintain the gradients].

### **Ion movement across the membrane generates electrical potential**

In the resting neuron Na<sup>+</sup>, K<sup>+</sup> and Cl<sup>-</sup> are continually moving through the membrane according to the balance of forces acting on each of them. Since ions are charged, they carry across the membrane **electric current**. These electric currents generate an electrical potential difference and the sum of these movements of charge is responsible for generating the membrane potential of the cell.

### **The resting membrane potential and the significance of ion permeability**

Sodium, potassium and chloride ions each have their own Nernst potentials (see table) but the resting membrane potential is different from each of them. Consequently K<sup>+</sup>, Na<sup>+</sup> and Cl<sup>-</sup> currents are constantly flowing across the membrane of the resting neuron and each of these currents tends to pull the membrane potential towards the respective Nernst potential of the ion in question. However, **the ability of each ion to influence the membrane potential depends upon its ability to pass through the membrane**, which in turn is the product of the **number of ion channels** through which it can pass and the **conductance** of those channels (i.e. the total conductance of the membrane for that ion per area of membrane). **Conductance (symbol g)** is just the measure of the ability of current to pass across the resistant membrane for any given force/potential difference. Conductance is measured in *Seimens* (often expressed as  $\square\text{S}/\text{cm}^2$  of membrane area). In the resting neuron the total conductance for K<sup>+</sup> (number of channels x individual channel conductance/cm<sup>2</sup>) is about 20 fold greater than the total conductance for Na<sup>+</sup>. Thus in the resting neuron, potassium is the dominant cation (positively charged ion) and the **resting membrane potential** is about -65 mV, closer to the Nernst potential for K<sup>+</sup> ( $E_K=-75\text{mV}$ ) than that for Na<sup>+</sup> ( $E_{Na}=+55\text{mV}$ ).

The membrane potential is thus determined by the movement of ions across the membrane through ion-selective channels. This results in a net negative charge on the inside of the cell relative to the outside (*the outside of the cell is, by definition zero potential*). The movement of the ions down their respective concentration gradients (**transmembrane current**) thus contributes to the resting membrane potential of the cell.

At the resting membrane potential of the neuron, the inside of the neuron is negative (say -65mV) because it contains more unbalanced negative charges than the outside (which is defined as 0mV). If the inside became less negative compared with the outside, we would say the membrane was becoming **depolarised**. If the inside becomes more negative, we say it is **hyperpolarised**.

### **Active transport of sodium and potassium ions across the membrane**

If the neuron did not act to correct for it, the concentration gradients of sodium, potassium and chloride ions would be expected to run down eventually and as a result the membrane would become depolarised. Indeed if the drug ouabain is applied to neurons the membrane potential does slowly depolarise and it was this observation that allowed the identification of the **Na<sup>+</sup>/K<sup>+</sup>-pump**. The Na<sup>+</sup>/K<sup>+</sup>-pump is a complex of proteins in the cell membrane that hydrolyses ATP and uses the energy of the hydrolysis to pump potassium into the cell against its concentration gradient. For each two potassium ions pumped in, the same protein pumps three sodium ions out of the cell (against the sodium concentration gradient). Since it hydrolyses ATP to provide the energy to concentrate Na<sup>+</sup> outside the cell and K<sup>+</sup> inside, the Na<sup>+</sup>/K<sup>+</sup>-pump is also referred to as the Na<sup>+</sup>/K<sup>+</sup>-ATPase and is an example of **primary active transport**.

When the Na<sup>+</sup>/K<sup>+</sup>-pump is operating in a neuron, it is the pump that sets and maintains the resting potential of the cell. Thus the Na<sup>+</sup>/K<sup>+</sup>-pump compensates for the reverse movement of sodium and potassium ions through the ion channels.

Thus the essential features in determining the membrane potential are; the concentration gradients of each of the ions, the activity of the Na<sup>+</sup>-K<sup>+</sup>-pump in maintaining those gradients in the long term and the membrane conductances for each of the ions. In a resting neuron the conductance for K<sup>+</sup> ( $g_K$ ) is small, but the conductances for the other ions are even smaller so at these times the K<sup>+</sup> current ( $I_K$ ) is the dominant current in determining the membrane potential. As a result of this the resting membrane potential is close to the Nernst potential for K<sup>+</sup>.

### **Passive electrical properties of neurons**

Electrical signalling in neurons involves ionic currents being switched on and off in one part of the neuron membrane and the resultant potential difference spreading to other parts of the neuron membrane via **local circuit currents**. For example, in the motor neuron, when **excitatory synapses** on the dendrites are activated, depolarising ionic currents switch on in the membrane under the synapse. Electrical current resulting from this will spread across the membrane of the motor neuron in a way that is determined by the **passive membrane properties** (or cable properties) of the cell. Understanding how transient potentials move in time and space is important because in the neuron cell body small depolarisations originating from synapses all over the neuron membrane add together in a process called **summation** at the **trigger zone of the neuron** (the membrane of the axon hillock). The sum of these small depolarisations at the trigger zone at any given instant determines whether the neuron will fire an action potential or not. This process is known as **synaptic integration**. Action potentials only fire when the membrane potential raises high enough to open a critical number of the **voltage-gated sodium ion channels** in the membrane. Passive membrane properties also explain how, once an action potential is initiated, it can propagate (move along) an axon.

The electrical properties of the axon (or a thin dendrite) can be compared to an insulated submarine telegraph wire and that is where the mathematical equations that explain the passive spread of membrane potential along an axon originated. Some properties of the neuron membrane don't change during the course of electrical signalling. The important elements of these **passive membrane properties** are:

1. **conductance of voltage-insensitive channels** (leakage channels)  
(the non-gated ion channels referred to above that are always open)
2. **membrane capacitance** (the ability of the plasma membrane to build up and hold charge, like an electrical capacitor)
3. **conductance of the cytoplasm** (this is particularly significant in the case of a long thin tube of membrane like the axon or dendrite of a neuron)

Each of these properties affects the spread of changes in membrane potential (*signals*) down the axon. Consider what happens when a micro electrode is pushed through the plasma membrane of the axon and a current is injected into the cell to cause the membrane surrounding the electrode to be depolarised. The local potential change at the site of the electrode is called the **electrotonic potential or local response**.

The current then spreads out along the inside of the axon (the *axoplasm*). As it does so the current is dissipated in two ways. Part of the current will initially cancel out the negative charge on the inside of the membrane. We say it discharges the **membrane capacitance**. Capacitance is a physical property of the lipid bilayer. Capacitors are devices widely used in the electronics industry. Whenever two electrical conductors are separated by a thin insulator there will be a measurable capacitance property. Charge will tend to accumulate on either side of the insulator because of electrostatic attraction to an excess of opposite charge on the other side. The thinner the insulator, the stronger the capacitance property (per square centimetre). This is because electrostatic attraction declines with the square of the distance of separation. Capacitors are useful in electronics because they store charge and change the rate that electrical potentials change in response to current changes. The same is true in neurons. In the case of the cell, the lipid bilayer is the insulator while the two conductors are the salty water of the extracellular fluid and the salty water of the cytoplasm. The charge will be in the form of ions. This means that as transmembrane currents start to flow they take extra time to alter the membrane potential because they must either discharge the negative 'capacitance charge' (during depolarisation) or recharge it (during repolarisation). Membrane capacitance can be represented by the symbol of a capacitor (two conductive plates separated by a non-conductive gap) in an electrical circuit that represents the passive properties of the membrane (Fig. 2).

Although the lipid bilayer provides a thin non-conductive gap that allows the membrane to act as a capacitor, it also contains some conductance elements, the voltage-insensitive ion channels (**non-gated ion leakage channels**). The remainder of the current will thus leak out of the axon through these channels (the resting **membrane conductance**) completing a circuit back to the point at which current was injected. The channels are far from perfect; relatively few ions can pass per second, so the membrane conductance is indicated in our equivalent circuit by the symbol for a resistor. **The conductance ( $g$ ) of an area of membrane is simply the inverse of its resistance ( $r$ , measured as Ohms-symbol  $\Omega$ ).**

Membrane has  
electrical capacitance



Ion channels in the  
membrane have resistance

The axoplasm is narrow  
and has resistance



*Electrical components of the axon that affect the spread of action potential signals.*

Each short segment of the axon length can thus be thought of as the equivalent of a resistor and capacitor connected in parallel across which a current is applied.

The injected inward current will begin to *discharge the capacitive charge on membrane*. The necessity of discharging of the plasma membrane slows down the spread of depolarisation down the axon or dendrite. Some axons have a relatively greater capacity to store charge than others, in such axons (particularly in small diameter axons), the action potential propagates more slowly.

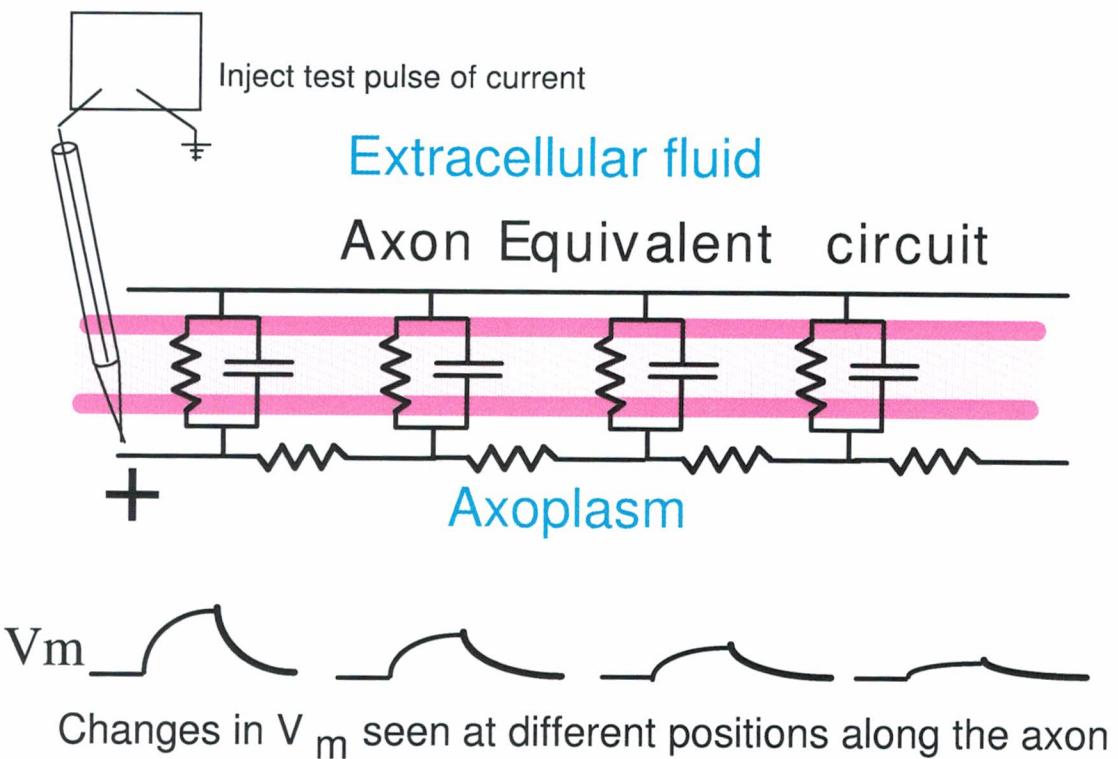


Fig 2.

Passive electrical properties determine the rate of propagation of action potentials in an axon. The figure above shows the lipid bilayer separating the extracellular fluid from the cytosol/axoplasm (electrical conductors separated by an insulator). Electrical components complete the equivalent circuit through which depolarising current flows along the axoplasm, and the return current in the extracellular fluid. The passive electrical properties modify the response of the membrane potential ( $V_m$ ) to a brief inward current at each point along the axon as indicated by the transient membrane potential traces ( $V_m$ ) at the bottom of the figure. Whether the brief depolarising inward current is generated artificially by the stimulator as shown, or naturally by the opening of voltage-gated  $\text{Na}^+$  channels (Hodgkin Cycle), the passive properties diminish the spread of changes in the  $V_m$  in the same way.

As the injected current moves along the inside of the axon it discharges the membrane capacitance and leaks out through the membrane conductance. In doing so it generates changes in the membrane potential. The axon is very thin and thus has much more resistance to the spread of current than the extracellular fluid so it is necessary to consider the **axoplasmic resistance**.

Axoplasmic resistance means that the amount of current flowing from the electrode to the site where membrane potential ( $V_m$ ) is measured (and therefore the change in membrane potential it produces) declines as we move along the axon away from the electrode. The axoplasmic resistance is shown between each membrane circuit unit in the equivalent circuit above (Fig 2). The relatively high resistance (low conductance) of the axoplasm leads to a decline in the amplitude of the signal with distance along the axon, while membrane conductance dissipates the local circuit currents and limits the distance that changes in the membrane potential ( $\Delta V_m$ ) can passively spread before they diminish to nothing.

The passive spread of membrane depolarisations (or hyperpolarisations) subject only to the effects of membrane conductance, membrane capacitance and axoplasmic resistance is known as **electrotonic conduction** (e.g. a small amplitude membrane potential change due to a synaptic current or injection of current through a micro electrode). Such currents fall off in amplitude exponentially with distance from their source.

### The action potential

Electrotonic conduction is no solution to the need to send electrical signals along axons that may be up to 1 metre in length. The solution that evolved was the action potential, a self-regenerating signal that is generated and maintained by the sequential opening of voltage-sensitive ion channels selective for (1) sodium and (2) potassium.

If the membrane of the neuron is depolarised sufficiently (to *threshold*) an action potential is triggered. The depolarisation causes **voltage-sensitive sodium channels** in the membrane to open and sodium ions enter the cell much more rapidly than when at rest. The sodium ions carry with them electrical charge (current) and cause the membrane to become even more depolarised. This added depolarisation opens even more voltage-sensitive sodium channels, causing the membrane to become even more depolarised. This self-reinforcing process ensures that the membrane potential rapidly rises from the negative resting potential to approach the Nernst potential for sodium (say +55mV).

However, the  $\text{Na}^+$ -driven membrane depolarisation does not persist for two reasons: (1) depolarisation eventually causes the open voltage-sensitive sodium channels slowly become *inactivated* (switch off) of their own accord and pass no more  $\text{Na}^+$  current; (2) the depolarisation also opens **voltage-sensitive potassium channels** that have a much higher conductance for potassium ions than the voltage-insensitive channels (the non-gated channels responsible for the resting  $V_m$ ). The voltage-sensitive  $\text{K}^+$ -channels are of the so called **delayed rectifier** type meaning that they open more slowly than the voltage-sensitive sodium channels after the membrane is first depolarised. The result of this delay is that the flow of  $\text{K}^+$  out of the cell occurs only after the depolarisation due to  $\text{Na}^+$  inflow has raised the  $V_m$  up to about +50mV and this is about the same time that the inward  $\text{Na}^+$  current is being shut off due to the delayed inactivation of the voltage-sensitive sodium channels. With the  $\text{Na}^+$  current out of the picture, the outward  $\text{K}^+$  current repolarises the membrane. See Fig. 3.

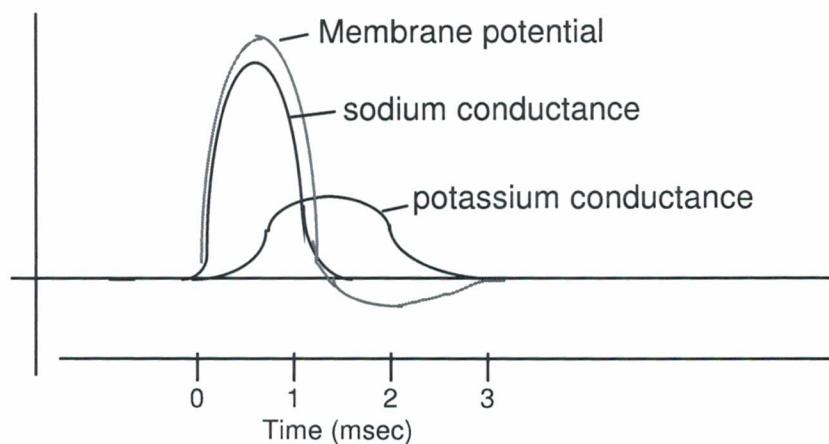


Fig. 3. Conductance changes contributing to the action potential

Thus, the **opening of voltage-sensitive sodium channels** causes the self-reinforcing depolarisation ( $\text{Na}^+$  current flows in), **then** (delayed) **inactivation** of the sodium

conductance and the (**delayed**) opening of the potassium channel conductance restores the negative membrane potential.

*Changes in conductance lead to changes in current which alter the membrane potential causing further changes in ion channel conductances.*

Immediately after the action potential there is a brief period when it is impossible to trigger a second action potential. This is called the **absolute refractory period** and it is due to the fact that the voltage-gated sodium channels remain **inactivated** and unable to open for a short time following the action potential. The **afterpotential** (a hyperpolarisation) that follows the action potential is due to the belated closing of some of the voltage-gated potassium channels. This afterpotential is responsible for the so called **relative refractory period** (or more precisely, **the period of reduced excitability**) of several milliseconds during which more depolarising current than normal is required to reach threshold for firing of a second action potential.

The unique feature of the action potential is the fact that it is **all-or-none**. Once a threshold is reached where the net inward current (flow of positive ions) exceeds the net outward current, the voltage sensitivity of the ion channel **gate** means that more and more sodium channels will open and the membrane will become more and more depolarised. The voltage dependent gating and delayed inactivation of the sodium current are due to structural features of the channel protein. Similarly the delayed opening of the potassium conductance is a unique feature of the structure of the delayed rectifier type of potassium channel protein. A field of intense investigation by physiologists and molecular biologists concerns the question of how structural features of the particular channel proteins might explain their characteristic types of gating.

The decline in concentration gradients of sodium and potassium ions that might otherwise follow a long series (a *train or volley*) of action potentials is avoided by the activity of the  $\text{Na}^+ \text{-K}^+$ -ATPase (the sodium/potassium pump). Please remember, *the rapid (few milliseconds) repolarisation phase of the action potential is caused by the activation of the voltage gated potassium channels. The pump is too way too slow acting to cause such fast changes in membrane potential.*

### **Electrotonic conduction and the spread of action potentials**

Electrotonic conduction (discussed previously) is important because it determines how fast an action potential can move along an axon: **the rate of passive spread of potentials is inversely proportional to both axoplasmic resistance and membrane capacitance**. Fast conduction of signals (by action potential propagation) is crucial to the proper function of neurons so organisms have evolved two approaches to overcoming the limitations in rate of passive spread imposed by electrotonic conduction. One solution is to reduce the axoplasmic resistance by *increasing the diameter of the axon* (e.g. the giant axon of the squid is up to 1mm diameter) to *reduce the axoplasmic resistance*. In mammals, an even more common and effective way is by *myelination* of the axons.

### **Axon myelination and saltatory conduction**

Myelination is a way of reducing the membrane capacitance of the axon. The capacitance of the membrane is critically dependent upon membrane thickness because the electrostatic interactions responsible decline with the square of the distance separating the charges (ions). The thickness of the axonal membrane is greatly increased by **myelination**. During development, nerve accessory cells (called **Schwann cells** in the PNS) wrap their plasma membrane like a thin tight bandage in a spiral fashion around each axon for stretches of about 200 micrometres. This **myelin sheath** increases the distance separating ions on the inside and outside of the axon, thus reducing the membrane capacitance charge.

Between each myelinated segment is a very short piece of bare axon membrane (a fraction of a micrometer long), the **node of Ranvier**. The action potential generated by the opening of voltage sensitive sodium channels at the node of Ranvier can then be *propagated* (spread) by the much more rapid electrotonic conduction that is possible through the adjacent myelinated segment (*the internode*) to the next node of Ranvier. The electrotonic potential spreads very rapidly (but with *diminishing amplitude*) through the myelinated segment from one node of Ranvier to the next, where the signal is amplified (by voltage-dependent opening of sodium channels). The depolarisation is then passed passively again to the next node. Since the action potential moves rapidly in jumps through the myelinated segments between the nodes of Ranvier, it is known as **saltatory (jumping) conduction**. Saltatory conduction has the advantages that it allows the action potential to travel much more quickly than would be possible with a continuously propagated action potential. Only a small fraction of the axon (the node segments) participate in active generation of an action potential (opening of sodium channels), so very much less energy is required to maintain the concentration gradients of the sodium and potassium ions (by the ATP-powered  $\text{Na}^+/\text{K}^+$ -pumps) in myelinated axons.

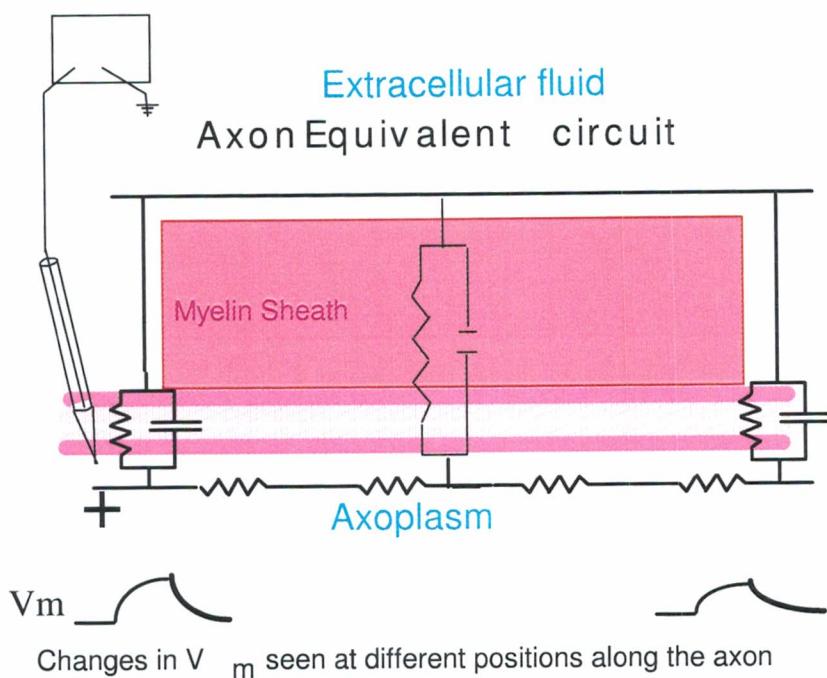


Fig. 4.

Myelination changes the passive electrical properties of the axon membrane, thus increasing the spread of the depolarising inward current, and reducing delays. Small portions of the axon membrane (Nodes of Ranvier) generate the depolarising inward current (Hodgkin Cycle). Whether generated artificially by a stimulator as shown, or naturally by the Hodgkin Cycle, the increased membrane resistance due to the thick, insulating myelin sheath means that the brief depolarising inward current can spread much further along the axon. The reduced tendency to store charge (capacitance) within the myelinated internode region means that the brief depolarisation moves more quickly from one Node of Ranvier to the next. Compare this with the previous figure for a non-myelinated axon.

### The neuromuscular synapse

#### Summary

The synapse between somatic motor neurons and skeletal muscle fibres is an excitatory chemical synapse; the transmitter is acetylcholine (ACh). The postsynaptic membrane contains a receptor for ACh, the **nicotinic ACh receptor (AChR)**. The nicotinic ACh

receptor is a *ligand-gated ion channel*, a transmembrane ion channel that is opened when ACh binds to the extracellular portion of the ion channel protein complex.

### The motor unit

Each limb muscle is innervated by a collection of motor neurons that are clustered together in the ventral horn of the spinal cord (the **motor neuron pool** of the muscle). The motor neuron pool may range from several to several hundred in number depending on the size of the muscle and the complexity of movements it engages in. The axon of each individual motor neuron branches within the muscle to form a number of synapses, each with a different muscle fibre. The muscle fibres innervated by a single motor neuron together with the motor neuron itself are known collectively as a **motor unit** since all the fibres are activated and contract simultaneously when an action potential comes down the axon of the motor neuron. The number of muscle fibres within a motor unit can vary between several dozen and several hundred, depending on the type of muscle fibre.

### The end plate potential

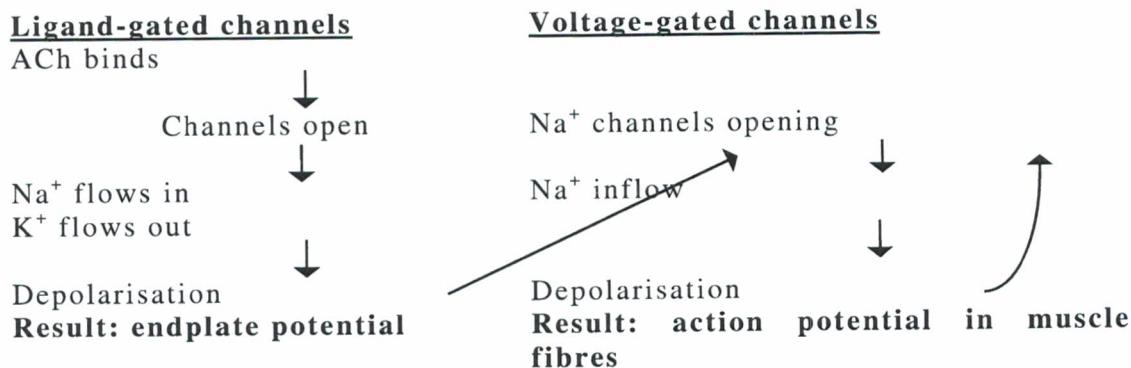
When the motor neuron is depolarised to threshold an action potential moves down the axon by saltatory conduction. When it reaches the non-myelinated nerve terminal the action potential spreads through all the branches on the nerve terminal where it triggers the release of ACh. The ACh rapidly diffuses across the *synaptic cleft* and binds to ACh receptors, opening the ion channel. The opening of the ACh-gated channel results in sodium entering the muscle fibre (inward sodium current) and a membrane depolarisation called the **End Plate Potential (EPP)**. In mammalian muscles the EPP is usually *suprathreshold* meaning that every time it occurs it triggers a postsynaptic action potential that rapidly depolarises the muscle fibre leading to contraction. Much of what is known about the release of transmitter during synaptic transmission has been inferred by studying the postsynaptic membrane potential changes produced by transmitter release.

The endplate potential is a very large depolarisation (about  $\Delta 70\text{mV}$ ; compared with  $\sim 1\text{mV}$  for synaptic potentials at central synapses) and consistently raises the  $V_m$  of the muscle fibre from its resting value of  $-90\text{mV}$  to well above threshold for a muscle action potential.

Release of transmitter from the presynaptic nerve terminal is very rapid and the burst of high concentration of ACh rapidly diffuses across the synaptic cleft and binds to the AChRs on the postsynaptic membrane, opening ion channels. However, much of the ACh in one burst (or quantum) of transmitter never reaches the AChRs on the postsynaptic membrane. After activating the AChRs immediately beneath the site of release, the ACh, which binds reversibly to the AChR, diffuses away and is rapidly degraded by the enzyme **acetylcholinesterase** (AChE). AChE hydrolyses ACh to acetate and choline. AChE thus ensures that the ACh receptor channels open only briefly. To study the membrane currents that are responsible for generating the postsynaptic potential, it is necessary to hold the membrane potential at a constant value as the AChRs are activated. The electronic apparatus that made this possible is known as the **voltage clamp**.

Voltage clamp studies showed that the **ACh receptor channels are permeable to both  $\text{Na}^+$  and  $\text{K}^+$**  (but not anions) and that when the AChR opens sodium flows in and potassium flows out of the cell. Even though the  $\text{K}^+$  outflow partially counteracts the  $\text{Na}^+$  inflow, more  $\text{Na}^+$  flows in than  $\text{K}^+$  flows out (consider the driving forces on each of the ions), resulting in the (*net inward*) endplate potential.

## At the neuromuscular junction



### **Transmitter release from the nerve terminal**

Within about 1ms of the nerve action potential reaching the axon terminal ACh is released, acts on AChR in the postsynaptic membrane and initiates the muscle action potential. The signal for the release of transmitter is the action potential depolarisation in the axon terminal but *neither the inward Na<sup>+</sup> current nor the outward K<sup>+</sup> current of the AP are sufficient to trigger ACh release*. Instead, **transmitter release is determined by Ca<sup>2+</sup> influx into the nerve terminal**. Ca<sup>2+</sup> like Na<sup>+</sup> is present in much higher concentration in the extracellular fluid than inside the cell. The arrival of the AP results in the opening of the presynaptic **voltage-sensitive Ca<sup>2+</sup> channels**, leading to a very localised Ca<sup>2+</sup> influx. The brief high intracellular pulse of Ca<sup>2+</sup> is thought to activate to Ca<sup>2+</sup>-binding proteins, leading to the release of ACh.

### **Quantal release of transmitter**

Intracellular electrical recordings from the postsynaptic membrane revealed that even in the absence of nerve stimulation small depolarisations of consistent amplitude called *miniature endplate potentials (mepps)* sometimes occur. Depolarisation of the nerve increases the frequency of these mepps but does not change their amplitude. When an action potential reaches the nerve terminal it normally results in an EPP that is composed of the sum of about 150 of these mepps (the mepp is much bigger than the depolarisation produced by the opening of a single AChR channel: coordinated opening of several thousand AChRs contribute to a mepp). The **vesicle hypothesis** holds that each mepp is the result of exocytosis from a *release site* on the nerve terminal of the ACh content of one 50nm-diameter synaptic vesicle containing a standard concentration of ACh. The calcium concentration does not change the size of the quantum of ACh released (as measured by the mepp amplitude) instead *the brief, localised calcium pulse is thought to increase the probability that a vesicle of transmitter will be released* at the release site. Since there are about 150 release sites per terminal this increases the total number of quanta released during each presynaptic action potential. The total number of quanta released following a single presynaptic action potential is known as the *quantal content* of the synapse.

### **Acetylcholine recycling**

As mentioned above, acetylcholinesterase (AChE) located in the postsynaptic infoldings rapidly hydrolyses ACh to choline and acetate. The neuron cannot synthesise choline and hence must recycle choline from the synaptic cleft. The presynaptic membrane contains transporter proteins that have a high affinity for choline (but not ACh) that bind to and internalise choline into the nerve terminal. Inside the nerve terminal an enzyme found specifically in cholinergic neurons, *choline acetyl transferase* transfers an acetate group to the choline and the ACh is repackaged into vesicles via the work of an active transport pump.

### **Pre- and post-synaptic block**

Certain drugs and toxins bind to and specifically block ion channels on either the pre- or post-synaptic membranes. For example, toxins from the venom of marine cone shell creatures bind to voltage-sensitive calcium channels and block transmitter release by preventing  $\text{Ca}^{2+}$  from flowing into the nerve terminal when the action potential depolarises the membrane. On the other hand,  $\alpha$ -bungarotoxin (from snakes) and curare (a plant product) bind to the AChR and prevent the endplate potential by preventing the opening of those channels in response to ACh release. Such natural blockers have helped us to learn much of what we know about synaptic function.

## **SYNAPTIC TRANSMISSION BETWEEN NEURONS**

Unlike the muscle fibre, most CNS neurons receive synaptic inputs from many other neurons, integrating them into a decision whether to fire action potentials. Individual neurons may:

1. Receive synaptic inputs from many other neurons from different parts of the brain. This is known as **convergence**.
2. Each synaptic input typically causes only a small synaptic potential ( $<1\text{mV}$ ).
3. Many of the synapses on each neuron are inhibitory rather than excitatory.
4. Have different types of transmitter receptors localized at different synapses on their plasma membrane. These include both **directly ligand-gated ion channel** type receptors (e.g. nicotinic AChR) and **second messenger-coupled receptors** that may cause slower, more subtle changes in the postsynaptic cell.

### **Excitatory postsynaptic potentials**

**Glutamate** is believed to be the major excitatory transmitter for central neurons. Most glutamate receptors are excitatory, meaning they cause inward (depolarising currents) called Excitatory Postsynaptic Currents (EPSCs). The transient depolarisation caused by these EPSCs is called the Excitatory Postsynaptic Potential (EPSP) and is akin to the EPP in the muscle fibre.

There are several different types of glutamate receptors that are ligand-gated ion channels; these are defined according to the drugs that specifically block them. These include AMPA types, NMDA types as well as a second messenger-linked glutamate receptor (Quisqualate- B type).

- The *AMPA type glutamate receptor channels are responsible for the rapid early phase of the excitatory postsynaptic potential (EPSP)*.
- *NMDA type receptors require both glutamate binding and depolarisation of the membrane before they open and are responsible for a late contribution to the EPSP.*

### **Inhibitory postsynaptic potentials**

The major **inhibitory transmitter** in the brain is **GABA** (gamma-aminobutyric acid). Another important inhibitory transmitter for the somatic motor neurons is glycine. Inhibitory neurotransmitters work mainly by **opening  $\text{Cl}^-$  channels** (sometimes  $\text{K}^+$  channels). Nernst potentials for  $\text{Cl}^-$  (and  $\text{K}^+$ ) are negative [ $E_{\text{Cl}} \approx -70\text{mV}$ ,  $E_{\text{K}} \approx -75\text{mV}$ ].

Opening of a ligand-gated  $\text{Cl}^-$  channel can inhibit depolarisation by:

1. Hyperpolarising a neuron towards the  $E_{\text{Cl}}$ .
2. The  $\text{Cl}^-$  conductance can "clamp"  $V_m$  at  $E_{\text{Cl}}$ , preventing inward currents from raising  $V_m$ .
3. The  $\text{Cl}^-$  conductance can act as a shunt or short circuit, dissipating the local circuit currents across the membrane before they reach the *trigger zone* at the axon hillock where action potentials are initiated.

GABA receptors have binding sites for benzodiazepines (e.g. Valium) and barbiturates: binding of either of these drugs to their binding sites on the GABA receptor increases

the affinity of GABA for its binding site, thus increasing the effectiveness of inhibitory inputs to neurons.

### Neuronal integration

- A single motor neuron can have up to 10,000 presynaptic inputs
- Neuronal integration is the decision of the neuron to fire or not to fire an action potential
- The **axon hillock** has a high concentration of  $\text{Na}^+$  channels and lower threshold (the **trigger zone**); action potentials (spikes) originate there.

### Temporal and spatial summation

Both EPSPs and IPSPs decline in amplitude with time and with distance along the dendrites from the source (the synapse), due to the *passive electrical properties* of the neuron.

Decline with time: measured by the **membrane time constant**. In neurons with a long time constant, EPSPs are slow to decay so sequential EPSPs can overlap and sum together to make a larger depolarisation. This is known as **temporal summation**.

Decline with distance along the dendrite: measured by the **length constant**. In neurons with large length constants EPSPs from distant synapses can more effectively add together at the trigger zone to reach threshold. This is known as **spatial summation**.

# Muscle Physiology

Atomu Sawatari

N104 Anderson Stuart Building

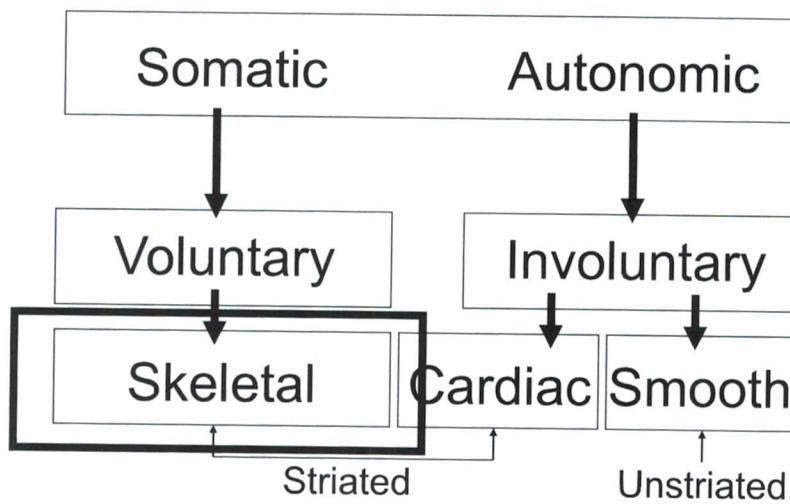
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## Outline

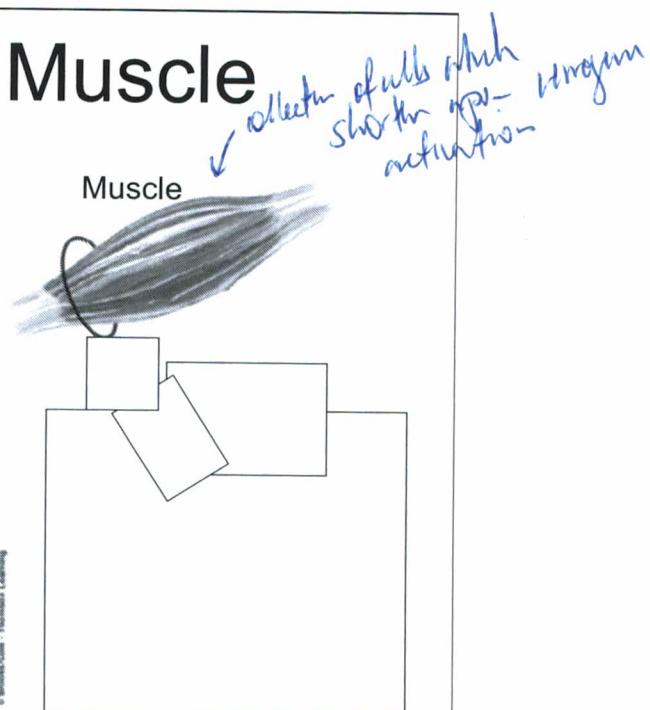
- Gross, cellular and molecular structure
  - gross level
  - cellular level
  - molecular level
- The molecular basis of muscle contraction
  - role of calcium
  - cross-bridge cycle
  - sliding filament theory of muscle contraction
- ECC and relaxation in skeletal muscle cells
  - Action potentials in the plasma membrane
  - Action potentials in the transverse tubular system
  - Signal for calcium release and uptake

# Action!



## Skeletal Muscle

- Voluntary
- Striated (striped)
- 40% of body weight
- Made up of muscle fibres

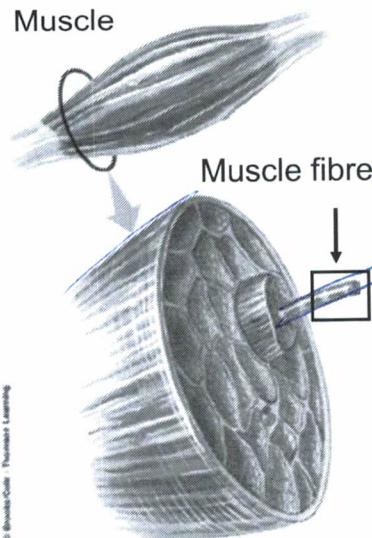


# Skeletal Muscle

- Voluntary
- Striated
- 40% of body weight
- Made up of muscle fibres

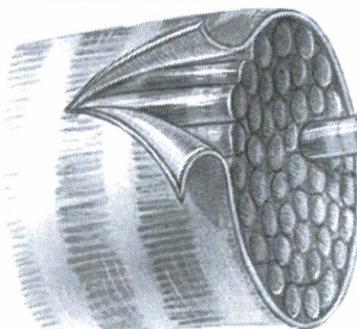
## Muscle fibres *striated*

- Skeletal muscle cell
- Multi nucleated: fusion of myoblasts during development
- Extend the length of the muscle
- Made up of myofibrils

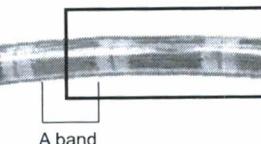


# Skeletal Muscle

Muscle fibre



Myofibril



## Myofibrils

- 80% volume of muscle fibre
- $1\mu\text{m}$  diameter, length of muscle
- Dark (A) bands, Light (I) bands

*strands of muscle fibres.  
striated*

*allows for contraction &  
relaxation.*

# Skeletal Muscle

## Myofibrils – Cytoskeletal Components

- A bands: thick filaments
- I bands: thin filaments only
- H zone: thick filaments
- M line: supports thick filaments
- Z line: supports thin filaments

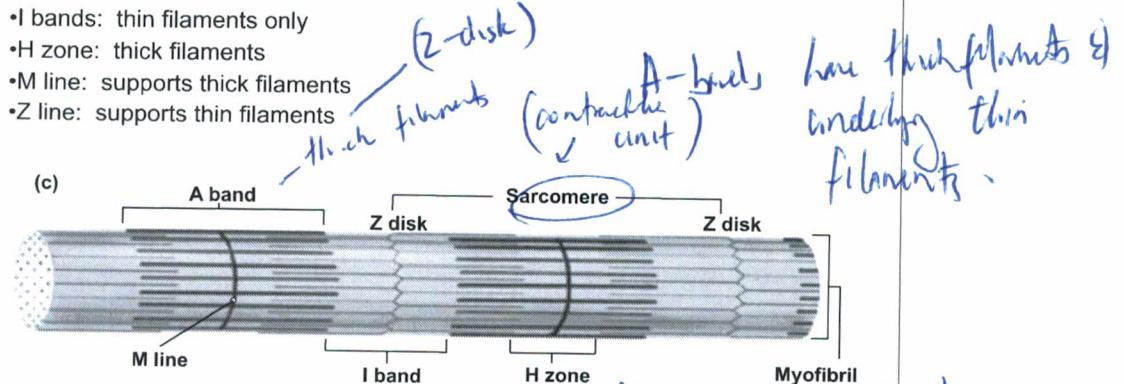
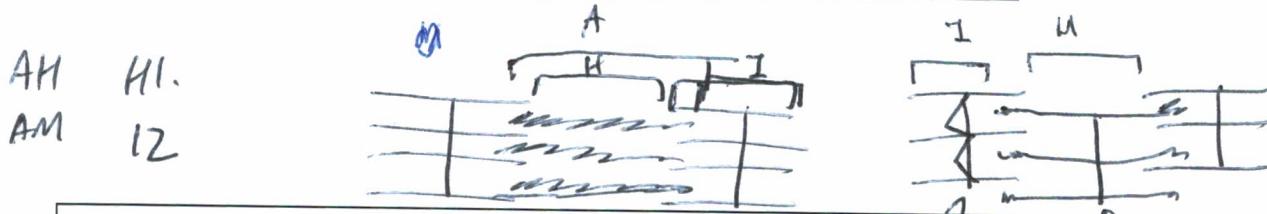


Figure 12-3c: Anatomy Summary: Skeletal Muscle

- Sarcomere: area between two consecutive Z lines

*Human Physiology: An Integrated Approach, 4e*  
By Dee Unglaub Silverthorn

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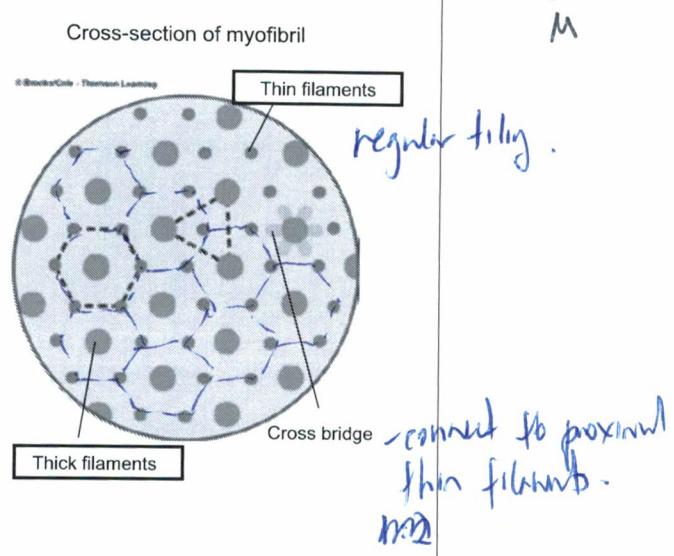


# Skeletal Muscle

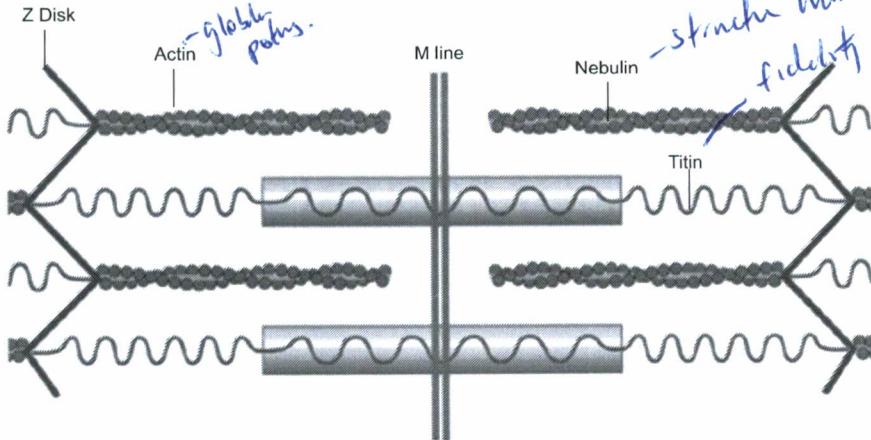
## Cross bridges

- Forms at overlap
- 1:2 thick/thin ratio:  
Single muscle fibre up to 16 billion thick and 32 billion thin filaments

## Filaments



# Skeletal Muscle



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# Skeletal Muscle

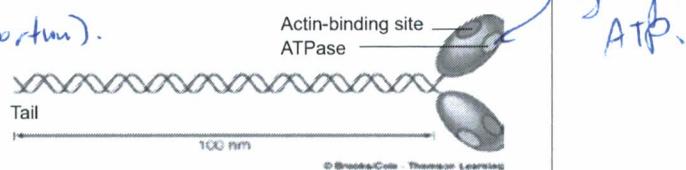
## Thick filaments: Myosin

### • Intertwined pairs

- one heavy chain (head (S1), neck, tail)
- two light chains: essential, regulatory

### • Globular head: (active portion).

- ATPase site
- actin binding site



# Skeletal Muscle

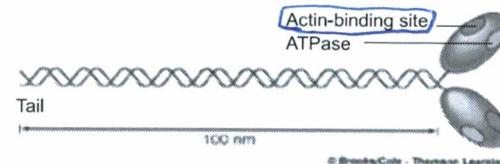
## Thick filaments: Myosin

- Intertwined pairs

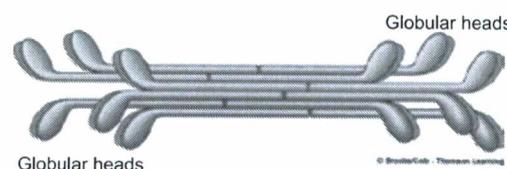
- one heavy chain (head (S1), neck, tail)
- two light chains: essential, regulatory

- Globular head:

- ATPase site
- actin binding site



- Bipolar assembly

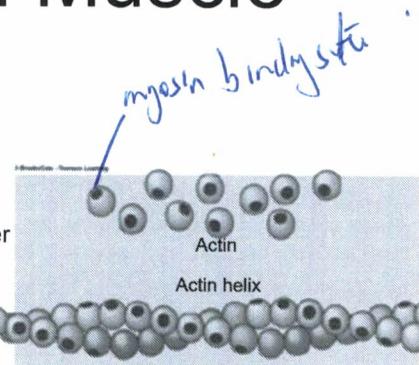


# Skeletal Muscle

## Thin filaments

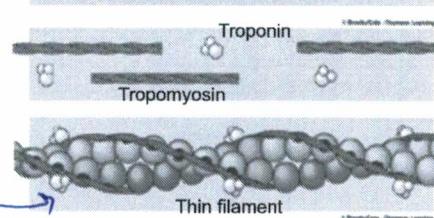
- Actin

- globe shaped molecule
- double stranded  $\alpha$ -helical polymer
- Forms cross-bridge with myosin



- Tropomyosin

- covers myosin binding site
- when Actin not bent.



- Troponin: protein complex

- I: binds actin
- T: binds Tropomyosin
- C: binds  $\text{Ca}^{2+}$

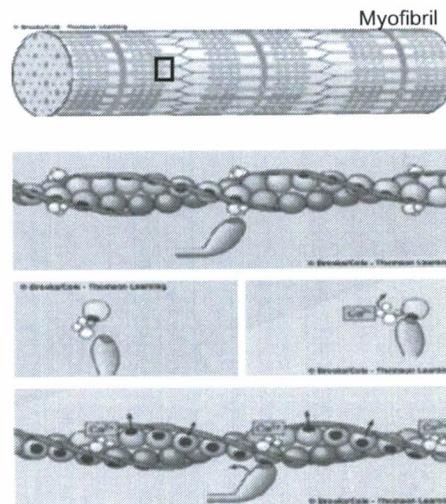
loves the  
binding site &  
loves th actin.

I - actin  
T - Tropomyosin  
C -  $\text{Ca}^{2+}$

# Skeletal Muscle

Cross Bridges:  $\text{Ca}^{2+}$

- Relaxed muscle fibre
  - No  $\text{Ca}^{2+}$ , no myosin binding
- Excited muscle fibre
  - $\text{Ca}^{2+}$  exposes myosin binding site
  - Actin-myosin binding initiates power stroke

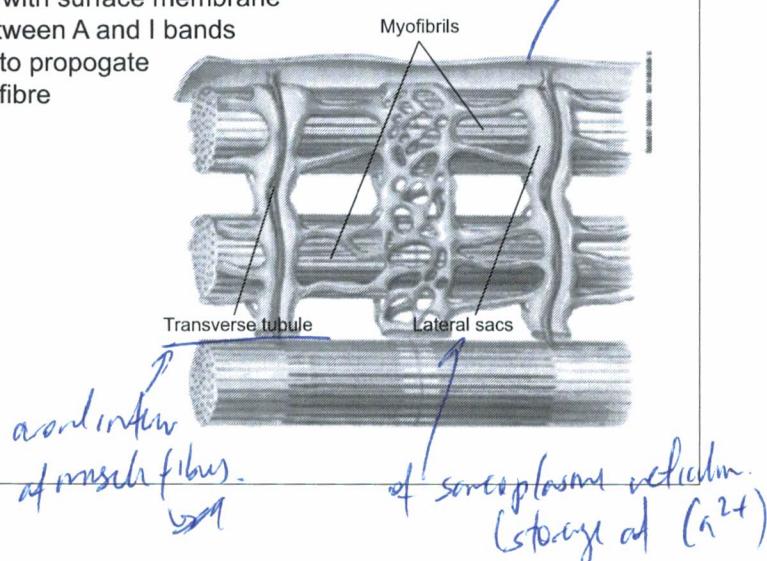


$\text{Ca}^{2+}$  binds to troponin, displaces tnn, tropomyosin (conformation change), exposes actin binding site, myosin binds to actin

# Skeletal Muscle

Cross Bridges:  $\text{Ca}^{2+}$  source

- Transverse tubule (TT)
  - Contiguous with surface membrane
  - Situated between A and I bands
  - Allows APs to propagate to center of fibre



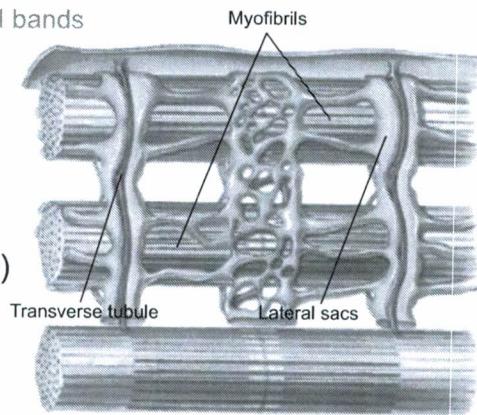
# Skeletal Muscle

## Cross Bridges: $\text{Ca}^{2+}$ source

- Transverse tubule (TT)

- Contiguous with surface membrane
- Situated between A and I bands
- Allows APs to propagate to center of fibre

- AP induces release of  $\text{Ca}^{2+}$  from the lateral sacs (terminal cisternae) of the sarcoplasmic reticulum (SR)



↑ release from lateral stores.

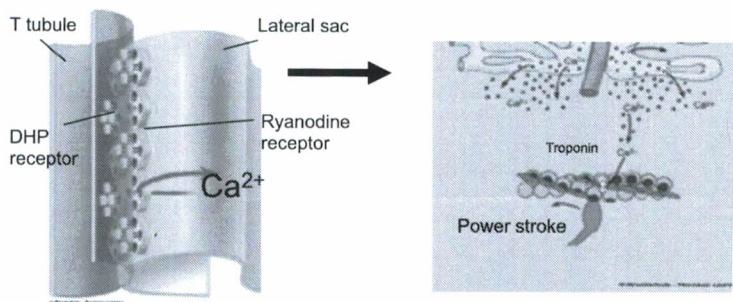
# Skeletal Muscle

## Cross Bridges: $\text{Ca}^{2+}$ source

- Tetrad of voltage sensitive L-type  $\text{Ca}^{2+}$  channels (DHP receptors) located on TT open adjacent ryanodine receptors (RR) on SR

- Stored  $\text{Ca}^{2+}$  in SR released to muscle fibre interior

physically linked to Ryanodine receptors

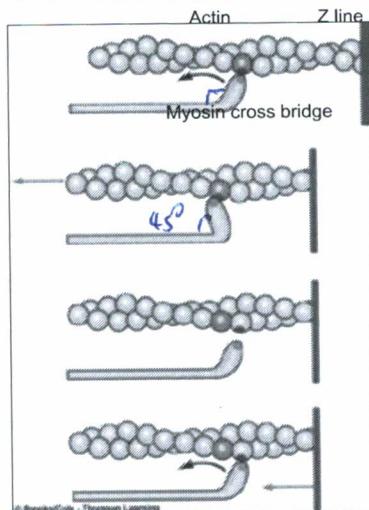


(second (n<sup>2</sup>) channel).

relieves inhibition of  $\text{Ca}^{2+}$  into cytosol.

# Skeletal Muscle

## Power stroke and cross bridge cycling



- Binding
  - myosin binds with actin

- Power stroke
  - cross bridge flexes

- Detachment
  - cross bridge detaches

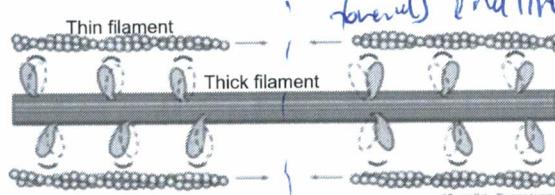
- Repeat
  - myosin rebinds with more distal actin

physical displacement of thick & thin protein.

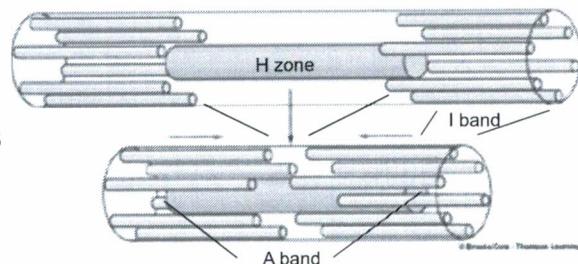
# Skeletal Muscle

## Power stroke and cross bridge cycling

- A more macroscopic view



- H zone and I bands shorten, but A bands remain unchanged



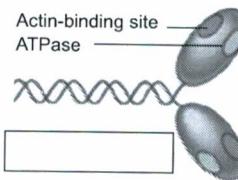
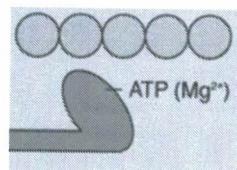
toward center  $\Rightarrow$  shortens filaments.

# Skeletal Muscle

## ATP powered cross bridge cycling

- Myosin ATPase

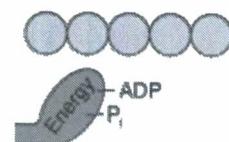
- Hydrolysis of ATP to ADP and Pi before binding to actin



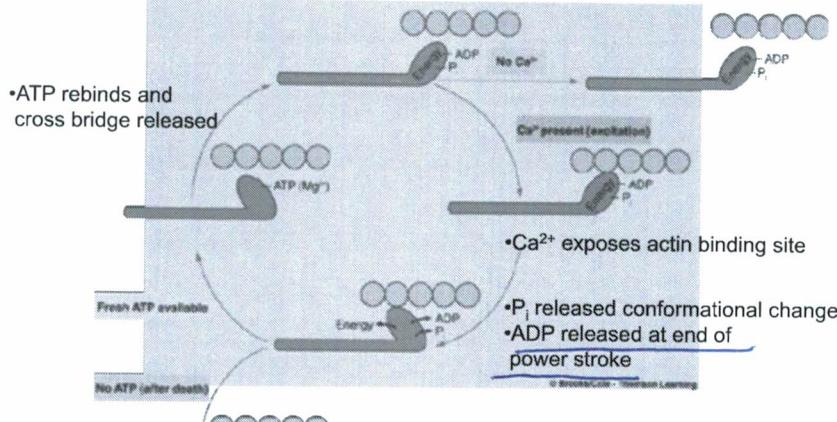
binds to ATP  
ADP + Pi

ATP allows release of myosin from actin hydrolysis.

- Released energy stored in myosin head



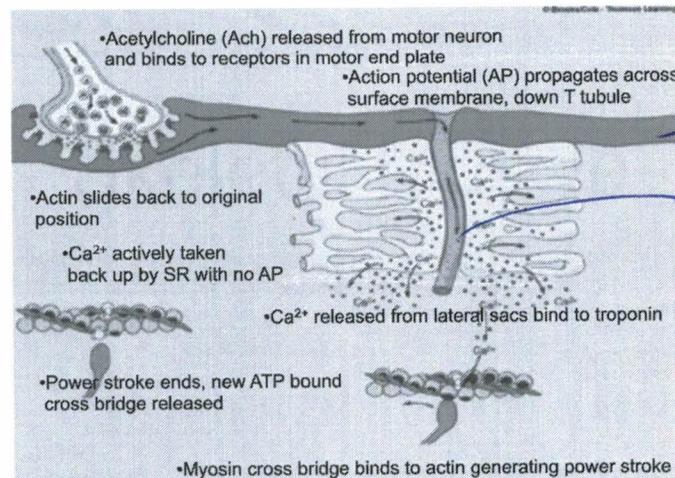
# Skeletal Muscle



- Rigor mortis

- Begins 3 to 4 hours after death
- myosin cross bridge remains attached due to lack of new ATP

# Skeletal Muscle



sarcoplasm .  
activates L-type  $\text{Ca}^{2+}$  channel,  
activatesryanodine receptor,  
releasing  $\text{Ca}^{2+}$ .

## Excitation-Contraction Coupling E.C.C.

# Skeletal Muscle

## Relaxation

- Cessation of activity, APs terminate
- AChE removes ACh from NMJ *Acetylcholinesterase*
- $\text{Ca}^{2+}$ -ATPase pump returns  $\text{Ca}^{2+}$  back into SR *(brings it stores)*
- Troponin-tropomyosin complex blocks myosin binding site *(on actin)*.
- Thin filaments return to resting position

*sliding filament model .*

# Structure and Function of Skeletal Muscle

- Gross, cellular and molecular structure
- The molecular basis of muscle contraction
  - The role of calcium
  - The cross-bridge cycle
  - Sliding filament theory of muscle contraction
  - Excitation-contraction coupling
  - Relaxation

## Objectives

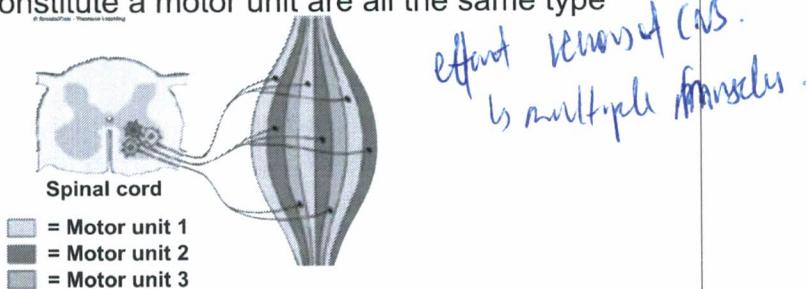
- Be able to describe the structure of skeletal muscle
  - at the gross level (whole muscle--muscle bundle--muscle cell--myofibril)
  - The cellular level (sarcomere, A- and I-bands, Z-line (or disc), H-zone, thick and thin filaments, myosin and actin).
  - the molecular level (myosin, actin, tropomyosin, troponin-1, -T, -C).
- What are t-tubules? How do they interact with the SR to release Ca<sup>2+</sup>?
- How does this interaction relate to muscle contraction and relaxation?
- How does Ca<sup>2+</sup> contribute to cross-bridge cycling? Explain the role of ATP in this interaction.
- How does the cross-bridge cycle relate to “sliding-filament theory” of muscle contraction?

# Skeletal Muscle Mechanics

## Number of fibres contracting

### Motor unit

- One motor neuron plus all innervated muscle fibres
- Fibres that constitute a motor unit dispersed throughout muscle
- Fibres that constitute a motor unit are all the same type

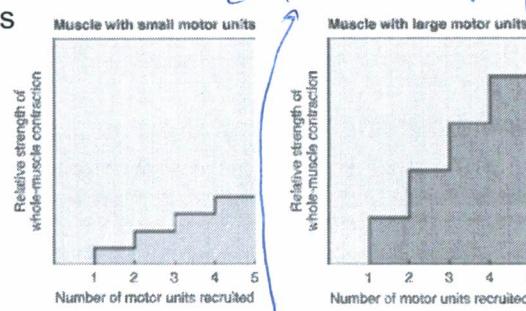


# Skeletal Muscle Mechanics

## Number of fibres contracting

### Motor unit

- Strength of contraction dependent on motor unit recruitment
- Number of fibres per motor unit and number of units per muscle vary depending on function
  - External eye muscles
    - Dozen fibres
  - Leg muscles
    - 1500 to 2000 fibres



more fibres  
by much.  
could be around  
with the works  
of muscle fibre

movement of eye, associated with less  
muscles.

# Skeletal Muscle Mechanics

Number of fibres contracting

## Motor unit

- Problem: Fatigue – inability to maintain muscle tension

- Solution: Asynchronous recruitment of motor units

- Alternating motor unit activity

- Does not happen in maximal contraction

# Muscle Physiology

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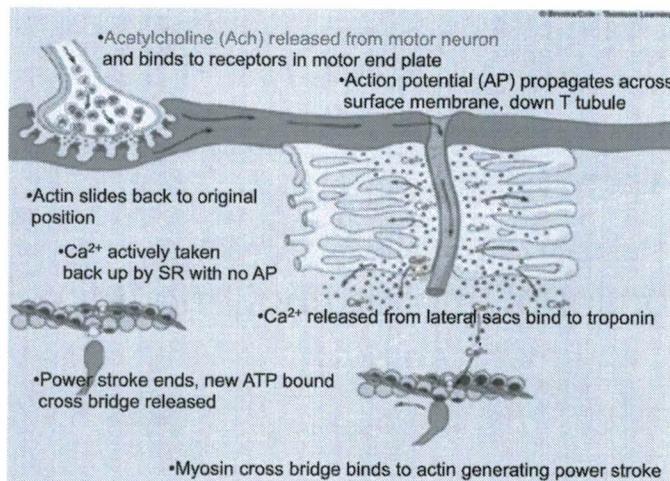
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## Outline

- Fatigue
- Different types of skeletal muscle fibres
  - Strength, speed, fatigue
- Factors influencing tension (muscle fibre)
  - Stimulation frequency
  - Length of fibre
  - Number of fibres
- Muscle mechanics
  - Isometric and isotonic contractions
  - Torque (limb)
- Muscle control
  - Coding of movement
  - Prosthetics

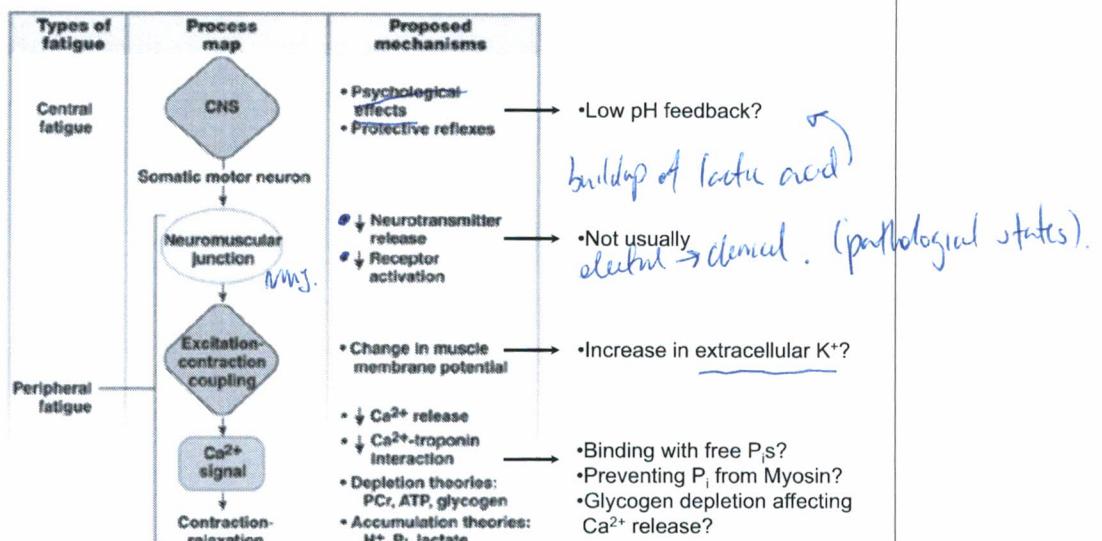
# Skeletal Muscle



## Excitation-Contraction Coupling

# Fatigue

*- not quite known.*



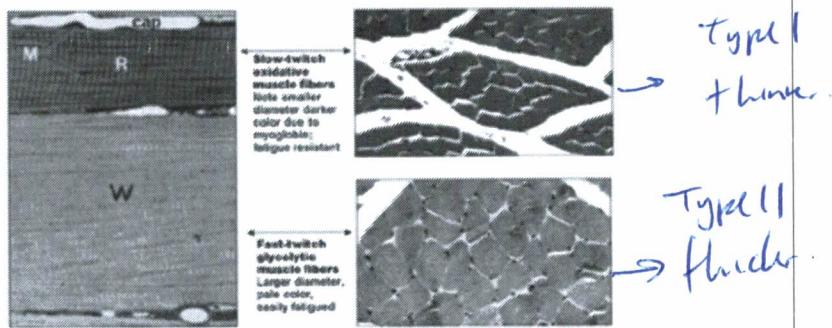
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*↓ ATP,  
 ↓ Ca<sup>2+</sup>,  
 phosphocreatine  
 used up.*

# Muscle Fibre Types

- Three different types of muscle fibres
- Based on strength, speed and fatigability
  - Slow twitch (type I)
  - Fast twitch (type IIA)
  - Fast twitch (type IIB/IIX)

all fibres recruit  
either motor units  
of same type.



Type I  
+ slower.

Type II  
faster.

# Muscle Fibre Types

## Speed

- Differences in components of contractile mechanism

Muscle	MHC	MLC	Phospholamban
Type I	-I	-1aS, -1bS	Y
Type IIA	-IIa	-1f, -3f	N
Type IIB	-IIb	-1f, -3f	N

Slow twitch

Fast twitch

moglobin,  $\text{O}_2$   
for ATP  
(red) Thinner  
(white) (glycogen &  
PCr, immediately  
convert to ATP)  
Thicker

Phospholamban:  $\text{Ca}^{2+}$ -ATP pump blocker

A pump removes  
 $\text{Ca}^{2+}$ , maintaining contraction,  
slower twitch.

# Muscle Fibre Types

## Fuel

- Regenerating ATP, the energy currency of cells

- Anaerobic

- PCr

- Glycolysis

]) ~~short, generate more ATP.~~  
~~buildup takes long time.~~

- Aerobic

- Glucose oxidation

]) ~~slow, generate more ATP.~~

# Muscle Fibre Types

## Strength

- Muscle fibre thickness

- Slow twitch generally thinner

## Fatigability

- Inability to maintain contractile activity to stimulation

- Central - anything before muscle

- Muscle - anything at muscle

Fatigability summary

Muscle	Fatigability	Color	Metabolism	Mitochondria	Glycogen
Type I	Resistant	Red	Oxidative	High	Low
Type IIa	Resistant	Red	Oxidative	Higher	Abundant
Type IIb	Fatigable	White	Glycolytic	Fewer	High

in vitro,  
can convert  
between the  
fibres

sug & phosphate  
for access ATP.

Type II → more fuel per contraction

Type I → oxidative process don't depend on  
local supply, not power, but can  
continuously contract for long time.

# Factors Influencing Tension

(by each fibre)

## Factors influencing tension

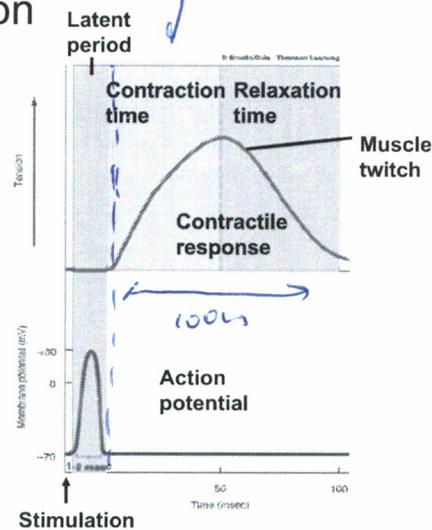
- Frequency of stimulation
- Length of fibre at onset of contraction
- Number of fibres contracting (order of fibres recruited to contract)

# Factors Influencing Tension

## Frequency of stimulation

- Twitches – contraction to single AP
- Small – actin binding incomplete
- Slow – latent period between AP and contraction
- Contraction and relaxation both dependent on  $\text{Ca}^{2+}$

optimal length

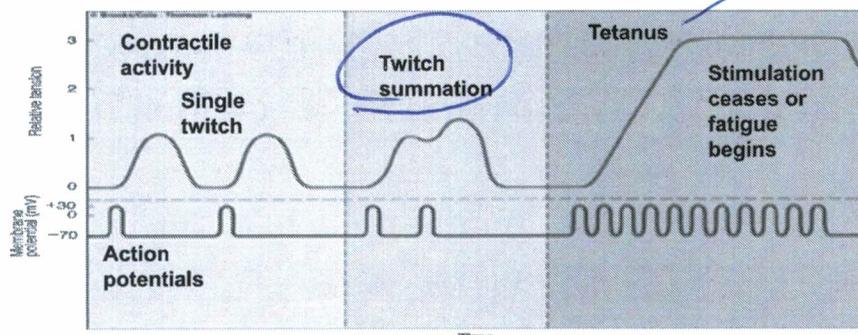


# Factors Influencing Tension

## Frequency of stimulation

- Twitch summation: "piggy backed" twitches
- Due to shorter duration of AP (1~2ms) compared to twitch (100ms)

- Tetanus: smooth, sustained contraction of muscle fibre
- Muscle fibre stimulated so it does not have chance to relax



Twitches relax in 2nd half.  
→  $\text{Ca}^{2+}$  release ( $\text{Ca}^{2+}$  release) &  $\text{Ca}^{2+}$  receptor overlap,  $\text{Ca}^{2+}$  remains in cytosol, allowing for summation of contraction

# Factors Influencing Tension

## Frequency of stimulation

- Twitch summation: works due to sustained elevation of cytosolic  $\text{Ca}^{2+}$

If AP's fire while  $\text{Ca}^{2+}$  still present in cytosol, myosin cross bridge binding on actin remain exposed allowing for continued contraction

In tetanus, maximum firing rates lead to maximum cytosolic levels which in turn lead to maximum contraction

change in frequency, change in contraction observed.

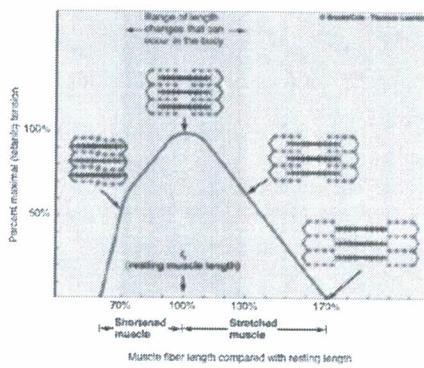
# Factors Influencing Tension

## Length-tension relationship

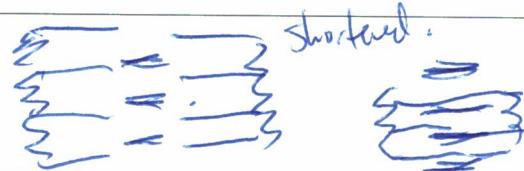
- Optimal length: length at which maximal overlap exists between thick and thin filaments resulting in maximal force
- Shorter or longer lengths will yield sub-maximal force
  - Shorter: mechanical interference
  - Longer: no overlap
- In vivo:* muscle length range limited to 0.7 to 1.3 times optimal length

Contractile proteins  
Contracture, tetanus (intact)  
Epineurium contains extracellular fluid.

• Passive force contribution

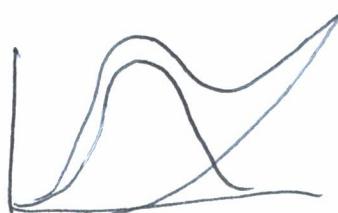
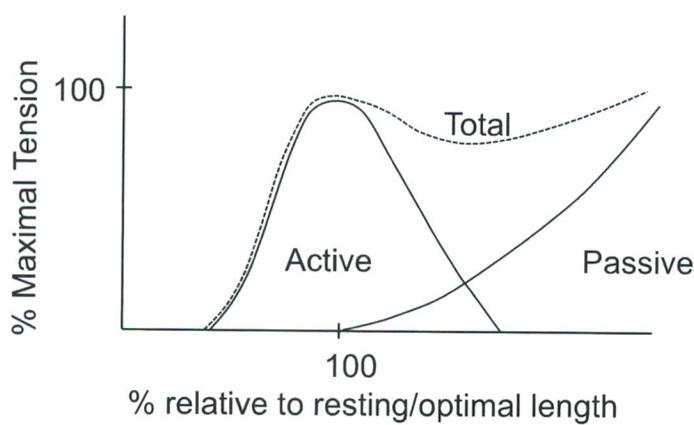


Thick & thin overlap for contractile.  
Stretch beyond overlap, little force  
(cannot physically bind)  
shortened, physically, actn (Z-stubs)  
have no passive force (no need spin for catch).



## Factors Influencing Tension

### Length-tension relationship

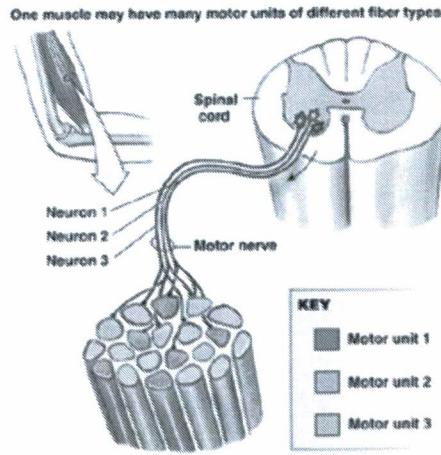


# Factors Influencing Tension

(Multiple fibres contracting)

## Motor unit

- One motor neuron plus all innervated muscle fibres
- Fibres that constitute a motor unit dispersed throughout muscle
- Fibres that constitute a motor unit are all the same type

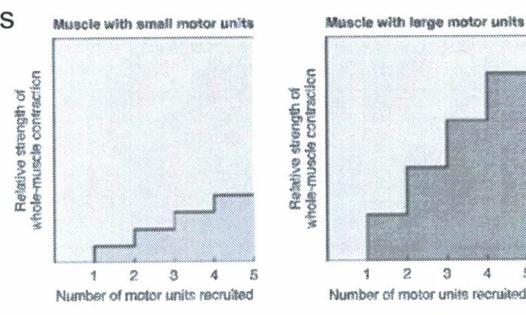


given muscle fibres  
innervated by 1 motor neuron (units can vary)  
max

# Factors Influencing Tension

## Motor unit

- Strength of contraction dependent on motor unit recruitment
- Number of fibres per motor unit and number of units per muscle vary depending on function
- External eye muscles
  - Dozen fibres
- Leg muscles
  - 1500 to 2000 fibres



# Factors Influencing Tension

## Motor unit

- Problem: Fatigue – inability to maintain muscle tension

- Solution: Asynchronous recruitment of motor units

- Alternating motor unit activity

- Does not happen in maximal contraction

- postural muscles, not many motor units needed,
    - recruits other proximal motor units.
    - into rhythmic fatigue manifestation

# Factors Influencing Tension

## Motor unit

- Problem: Regulating force of contraction

- Solution: Fixed order of recruitment

- Type I
  - Type IIa
  - Type IIb

- small motors, use type I  
(eg fingers).*

# Skeletal Muscle Mechanics

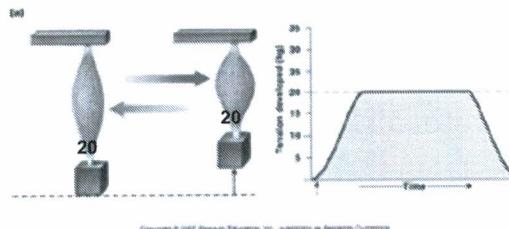
What kind of contractions can skeletal muscles make?

## Isotonic contractions

lift slowly  
liftable.

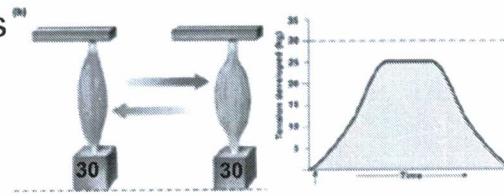
- Tension results in movement
- Sub-maximal contraction
- Load dependent

maintain level of tension.



## Isometric contractions

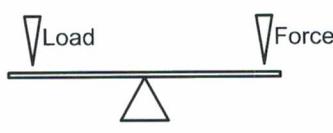
- Tension develops at constant muscle length
- Maximal (load) or sub-maximal (posture)



length of muscle not changing yet force still being exerted.

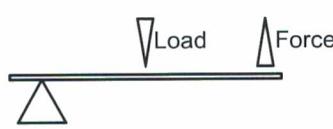
# Skeletal Muscle Mechanics

Lever systems of muscles, bones, and joints



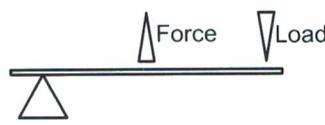
### Class One Lever

Force: posterior neck muscle  
Load: face  
Fulcrum: atlanto-occipital joint



### Class Two Lever

Force: gastrocnemius  
Load: body  
Fulcrum: ball of foot



### Class Three Lever

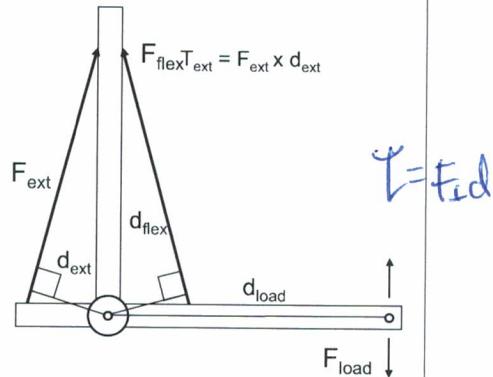
Force: bicep  
Load: object in hand  
Fulcrum: elbow

rotational force

## Skeletal Muscle Mechanics

Lever systems of muscles, bones, and joints

- Hinge joint = fulcrum
- Torque: Force that rotates joint
  - Equal to pull (force) x the length of the moment arm (distance from fulcrum to force location)
  - Upward force: bicep  
 $T_{flex} = F_{flex} \times d_{flex}$
  - Downward force: forearm + load  
 $T_{load} = F_{load} \times d_{load}$



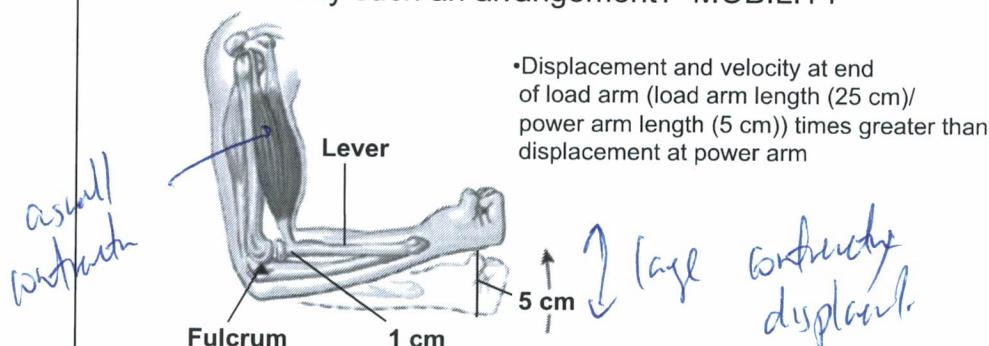
$T_{flex} > T_{load}$ , isometric.

$T_{flex} = T_{load}$ , isokinetic

## Skeletal Muscle Mechanics

Lever systems of muscles, bones, and joints

Why such an arrangement? MOBILITY

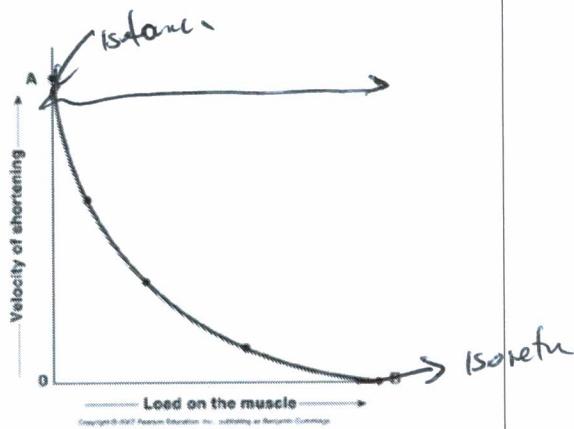


$\Rightarrow$  mobility .

# Skeletal Muscle Mechanics

## Load-velocity relationship

- The smaller the load, the faster the shortening of a single or constant number of fibres
- Velocity maximal with zero load, zero contractile force
- Velocity falls to zero when load cannot be overcome with tetanic tension (isometric contraction)



# Skeletal Muscle Mechanics

- Twitch vs tetanic contractions: effect of stimulation frequency
- Length-tension relationship
- Isometric and isotonic contractions
- Motor unit recruitment

## Objectives

- Use your understanding of nerve action potential to define graphically the time course between motoneurone activation, neuromuscular junction activation, muscle activation and muscle force production.
- Predict the relative amount of force produced by a muscle under different physical and chemical conditions by drawing on your understanding of the sliding filament theory and the cross-bridge cycle.

## Skeletal Muscle Control

### Voluntary movement

- Purposeful
- Affected by experience and learning
- Can be generated internally

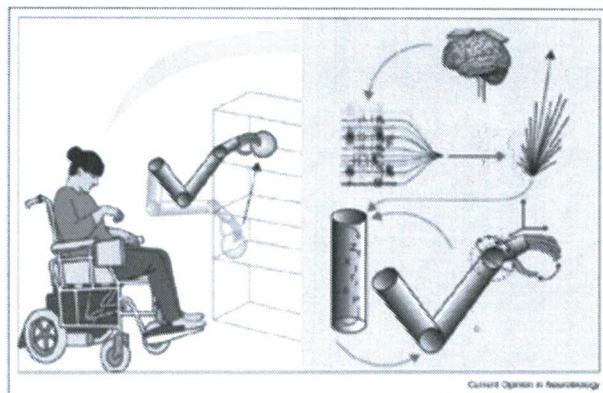
# Skeletal Muscle Control

Primary motor cortex: movements or muscles?

- Topography
- Single neurons: direction and amplitude of force; not displacement (Evarts)
- Population vectors: direction of movement (Georgopoulos)

# Skeletal Muscle Control

Prosthetics



(Georgopoulos and Carpenter, 2014; figure and legend from Courtine et al., 2013)

(3)

Lecture 3

# Muscle Physiology

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Figures in this lecture are presented courtesy of Brooks/Cole-Thompson Learning unless otherwise stated

## Outline

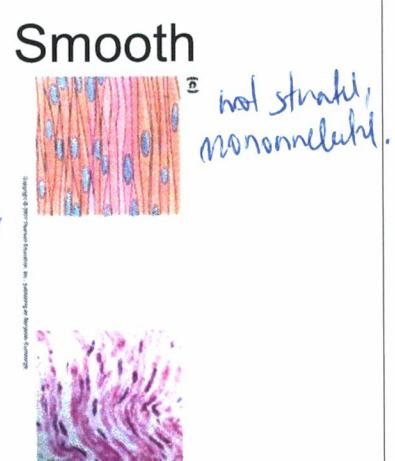
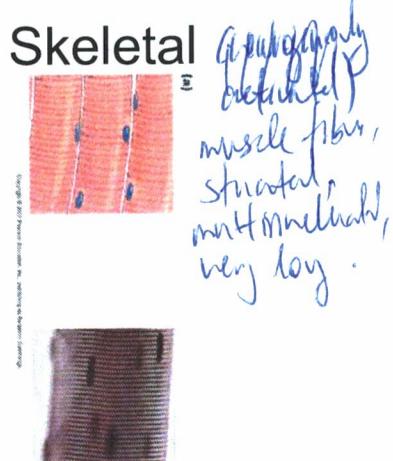
- Introduction to smooth and cardiac muscles
  - Characteristics
  - Differences relative to skeletal muscle
    - Structure
    - Contraction mechanism
    - Activation
    - $\text{Ca}^{2+}$  source
    - Termination

# Smooth Muscle

- Can be characterized by
  - Location
    - Vascular
    - Gastrointestinal
    - Urinary
    - Respiratory
    - Reproductive
    - Ocular (pupil muscle)
  - Contraction Pattern
    - Phasic → signal (not linked to nervous)
    - Tonic → sphincter, remain contracted until signals come to relax.
  - Means of communication with neighboring cells

## Smooth Muscle Differences

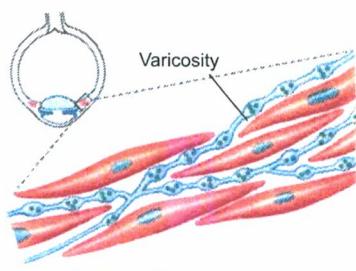
### Structure



# Smooth Muscle Differences

## Smooth

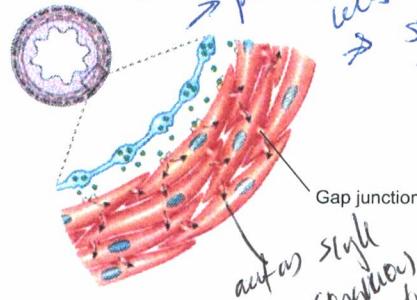
- Multi Unit *actually independently*



- Neural activation
- Muscle of the iris, piloerector, uterus

*N/s contraction*

- Unitary



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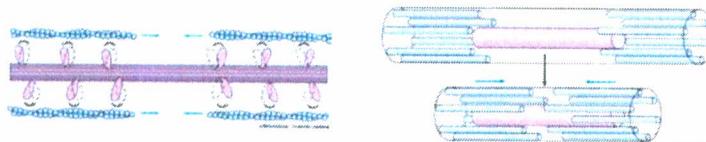
- Syncytia - Single entity for synchronous contracts
- Linked by gap junctions
- Visceral:
  - gastrointestinal, reproductive, vascular

made of one cell, linked gap junc.  
→ picn. struc. connec.  
cells. → sig trans.  
↓ other cells  
linked by gap junc.  
e.g. rhythmic  
synchronous  
contraction  
present in viscera

# Smooth Muscle Differences

Differences in contraction mechanism

## Skeletal



## Smooth

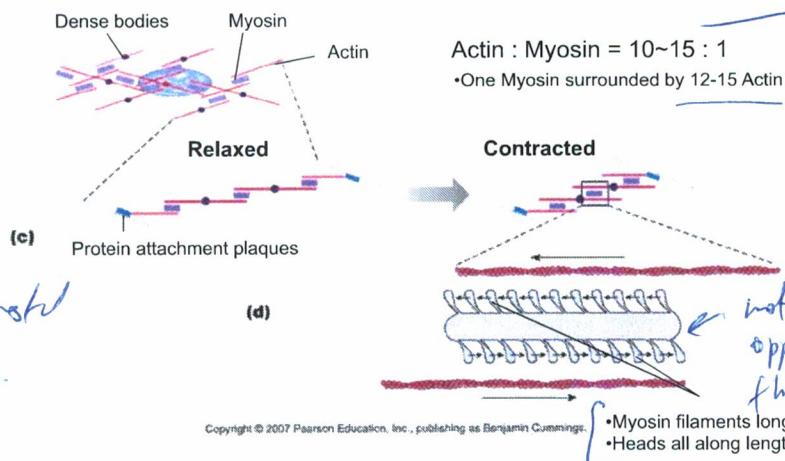


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# Muscle Types

## Differences in contraction mechanism

dense bodies not at 2-lines.



# Muscle Types

## Differences in contraction mechanism

### Smooth

- Full force contraction at greater percentage of length

- Overlap of thin and longer thick filaments
- Shorter resting length

- \* •Stress relaxation response:

- Rearrangement of cross bridges

↳ Can't relax, but muscle becomes contracted.

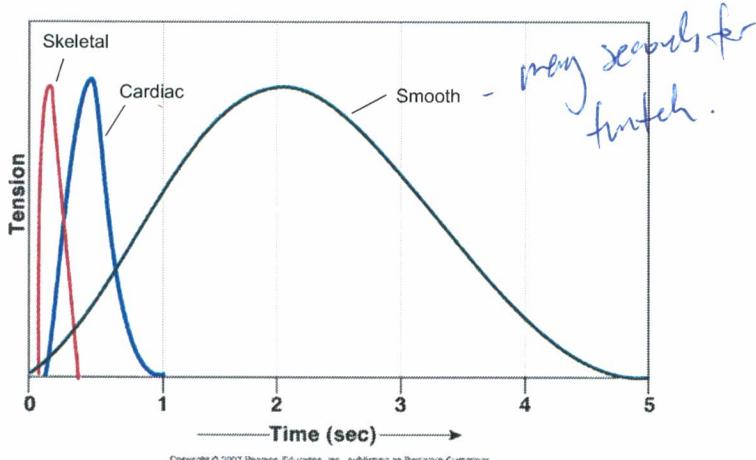
length & contractile force.

broad range of optimal length

↓ don't overlap of filaments & large actin.  
or worse less ATP, remain contracted for longer.

# Muscle Types

Differences in contraction mechanism

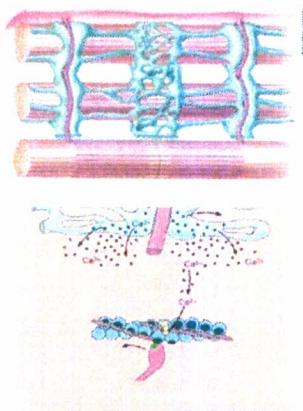


# Muscle Types

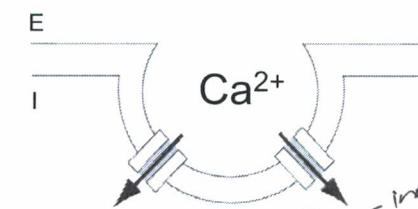
Differences in  $\text{Ca}^{2+}$  source

Skeletal + Smooth

$\text{Ca}^{2+}$  stored in latent stores  
(IC)



Smooth



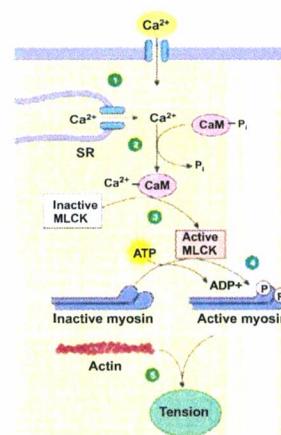
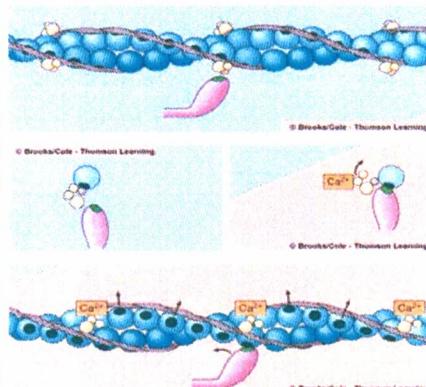
- Caveoli: rudimentary T-tubule
  - Influx of  $\text{Ca}^{2+}$  via L-channels
  - Force dependent on  $[\text{Ca}^{2+}]_e$
- From SR
  - IP<sub>3</sub> (Phospholipase C cascade)
  - RyR (Ca<sup>2+</sup> induced Ca<sup>2+</sup> release)

IP<sub>3</sub> receptor (like in skeletal muscle)

# Muscle Types

Differences in contraction mechanism

## Skeletal



## Smooth

- 1 Increased intracellular  $\text{Ca}^{2+}$
- 2  $\text{Ca}^{2+}$  binds to CaM
- 3 CaM-CaM activates MLC kinase (MLCK)
- 4 MLCK phos. MLC ↑ATPase activity
- 5 Creates muscle tension

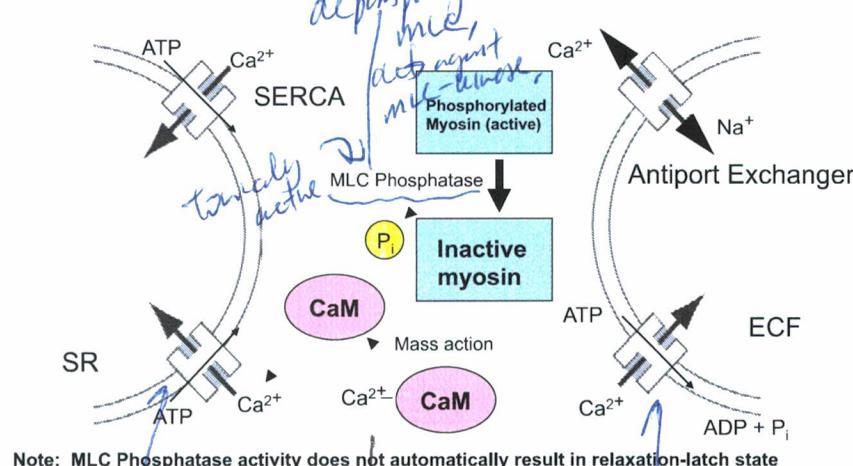
act on thick filaments instead of calmodulin. myosin-light chain kinase phosphorylates here instead of actin. ATP affinity allowing contraction b/c sw.

# Muscle Types

Differences in termination

## Skeletal + Smooth

## Smooth



Note: MLC Phosphatase activity does not automatically result in relaxation-latch state

Ca<sup>2+</sup>, ATP pump.

mobility of CaM  
= rebind in MLC

mass action decomp.  
in  $\text{Ca}^{2+}$

# Muscle Types

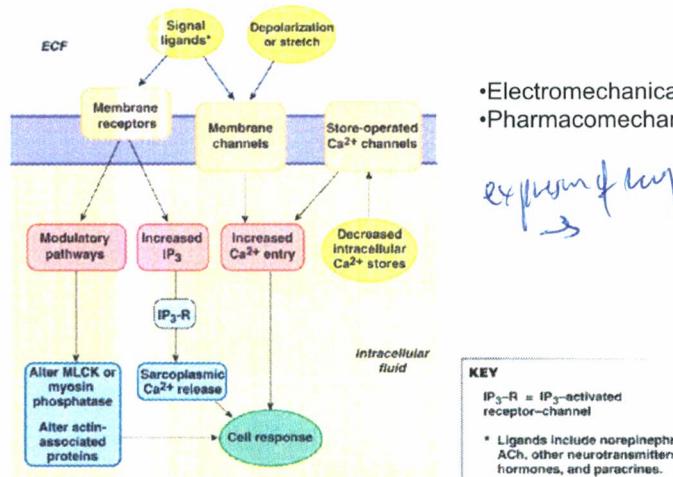
## Differences in termination

- MLCP always on: MLCK activity critical
- Ca<sup>2+</sup> sensitivity determined by MLCP activity
  - If MLCP activity increases (e.g., via paracrine signalling) contraction process is desensitized: contraction force decreases (even with no change in [Ca<sup>2+</sup>])
  - Sensitized if MLCP activity decreases

multiple levels of regulation.

# Muscle Types

## Differences in activation



- Electromechanical coupling
- Pharmacomechanical coupling

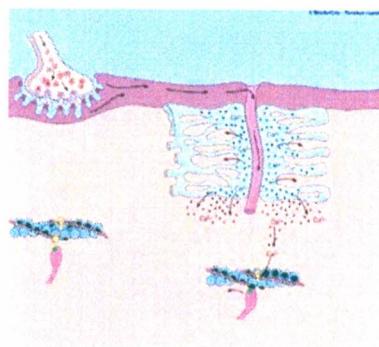
act on 2 very  
messengers w/o  
changing  
membrane potential.

# Muscle Types

Differences in activation

## Skeletal

- Neurogenic activation



## Smooth

- Neurogenic activation

- Autonomic nerve fibres
  - Can be controlled by sympathetic and/or parasympathetic activation
- Diffuse junctions/contact junctions
  - APs not necessary
  - Modulatory in unitary muscle
  - Varicosities instead of endplates

*effektiv axos.*

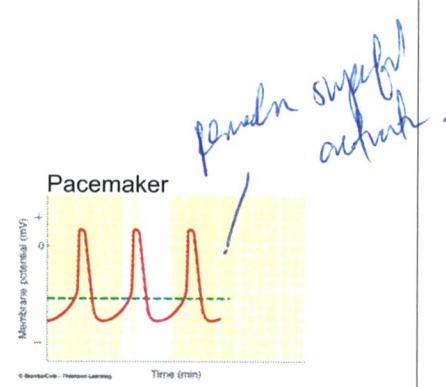
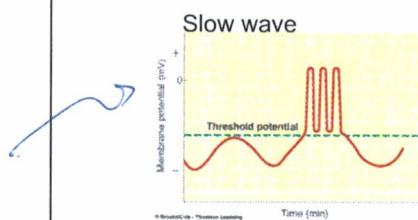
# Muscle Types

Differences in activation

## Smooth

- Myogenic activation

- Unitary muscle
- Slow wave, pacemaker waves



• Slow wave: variable active  $\text{Na}^+$  pumping-fire when threshold reached

• Pacemaker: variable passive permeability to cations-always reach threshold

*extra refraction.*

# Muscle Types

Differences in activation

## Smooth

- Hormone/Paracrine dependent excitation/inhibition

- Can be direct or indirect
  - Induce contraction by releasing  $\text{Ca}^{2+}$  from SR
  - Inhibit contraction by activating  $\text{Ca}^{2+}$  pumps
  - E.g., histamine constricts smooth muscle airways
  - E.g., NO affects blood vessel diameters

in blood  
o general effector  
smooth muscle.  
- & Ca<sup>2+</sup> increase act  
- deeper contraction

- Mechanical stimulation

- Stretch dependent depolarization: visceral muscle

# Muscle Types

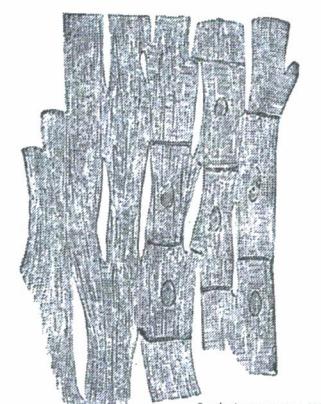
## Cardiac

### Properties

- Three muscle types: atrial, ventricular, excitatory/conductive

- Atrial and ventricular muscle
  - Striated
  - Syncytia
    - Intercalated disks
    - Gap junctions

Syncytial  
contraction.



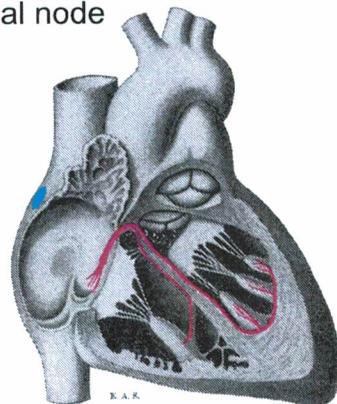
mononucleated, regen'te  
Smooth musc.

# Muscle Types

## Cardiac

### Properties

- Myogenic: AP initiated at sinoatrial node
- Plateau potentials
  - 200ms (atrium) to 300ms (ventricle)
  - Fast  $\text{Na}^+$ , slow  $\text{Ca}^{2+}$  channels,
  - decrease in  $\text{K}^+$  permeability
- Refractory period as long as AP
  - Prevents tetanus



Gray's Anatomy, plate 501

fatch contraction,

## Summary

TABLE 12-3 Comparison of the Three Muscle Types

	SKELETAL	SMOOTH	CARDIAC
Appearance under light microscope	Striated	Smooth	Striated
Fiber arrangement	Sarcomeres	Oblique bundles	Sarcomeres
Fiber proteins	Actin, myosin; troponin and tropomyosin	Actin, myosin, tropomyosin	Actin, myosin; troponin and tropomyosin
Control	• Voluntary • $\text{Ca}^{2+}$ and troponin • Fibers independent of one another	• Involuntary • $\text{Ca}^{2+}$ and calmodulin • Fibers electrically linked via gap junctions	• Involuntary • $\text{Ca}^{2+}$ and troponin • Fibers electrically linked via gap junctions
Nervous control	Somatic motor neuron	Autonomic neurons	Autonomic neurons
Hormonal influence	None	Multiple hormones	Epinephrine
Location	Attached to bones; a few sphincters close off hollow organs	Forms the walls of hollow organs and tubes, some sphincters	Heart muscle
Morphology	Multinucleate; large, cylindrical fibers	Uninucleate; small spindle-shaped fibers	Uninucleate; shorter branching fibers
Internal structure	T-tubule and sarcoplasmic reticulum	No T-tubules; sarcoplasmic reticulum reduced or absent	T-tubule and sarcoplasmic reticulum
Contraction speed	Fastest	Slowest	Intermediate
Contraction force of single fiber twitch	All-or-none	Graded	Graded
Initiation of contraction	Requires input from motor neuron	Can be autorhythmic	Autorhythmic

## Objectives

*Smooth muscle:*

- Describe the function of dense bodies, intermediate filaments and caveoli.

*multifunctional & unifocal gap junctions.*

- List the two main types of smooth muscles, the organs whose function they support, and compare their different modes of excitation.

*syncytium*

*Cardiac muscle:*

- Describe the function of intercalated disks in the excitation process.

*fast conduction*

- Describe the time course between the cardiac cell action potential and contraction.

*long refractory period*

- Explain the significance of the long refractory period for heart function.

*prevents tetanus*

# Muscle Physiology

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## Types of Movement

- **Reflex movements:** e.g. Withdrawal from pain, cough, etc.  
*to brain / away*  
Initiated via sensory receptors, integrated at the spinal cord or brain stem.
- **Rhythmic movements:** e.g. walking, breathing  
Initiated and terminated voluntarily, integrated in spinal cord (central pattern generators) with input from higher centres.  
*my body not feel pain until later.*  
*don't need top-down control.*
- **Voluntary movements:** e.g. Write, jump, speak, etc.  
Initiated by external stimuli or at will, integrated in cerebral cortex. Improve with practice, may become automatic

*newton's crntb*

## Outline

- Skeletal muscle control
  - Voluntary movements
- Disease states (examples)

*\* interact with the environment.*

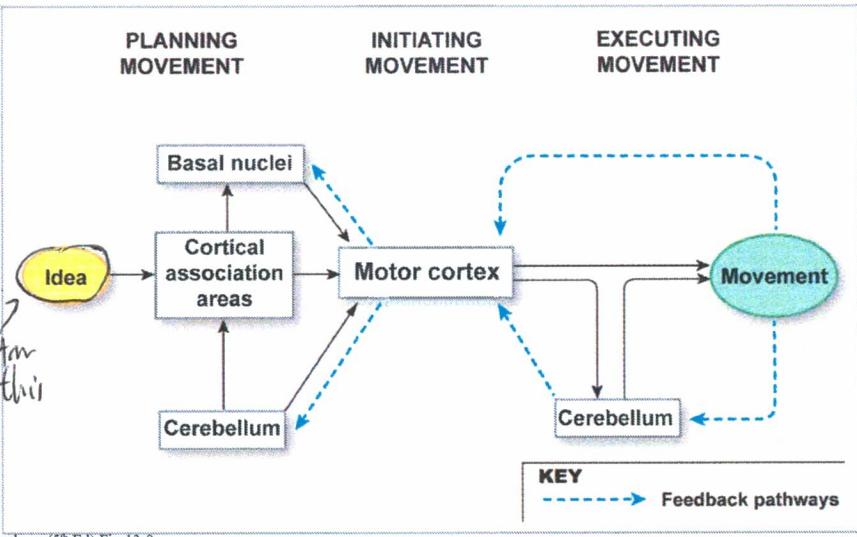
## Skeletal Muscle Control

### Voluntary movement

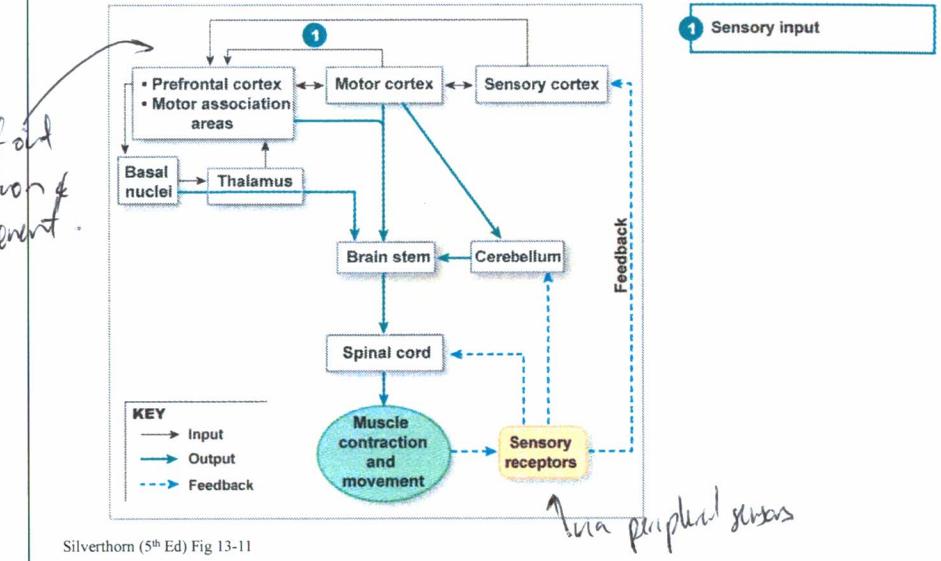
- Purposeful
- Affected by experience and learning
- Can be generated internally

*with experience, our movements become more refined & efficient.*  
*manifest internally & externally.*

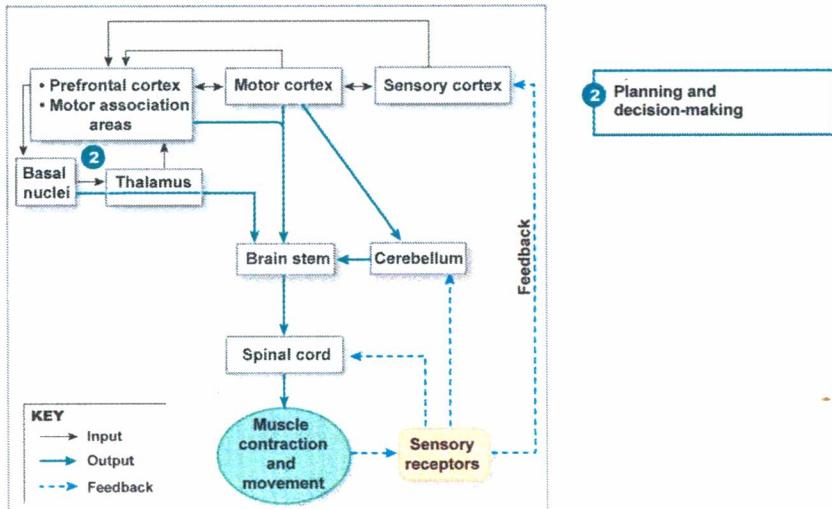
## Generation and Control of Voluntary Movement



## Generation and Control of Voluntary Movement



## Generation and Control of Voluntary Movement



## Generation and Control of Voluntary Movement

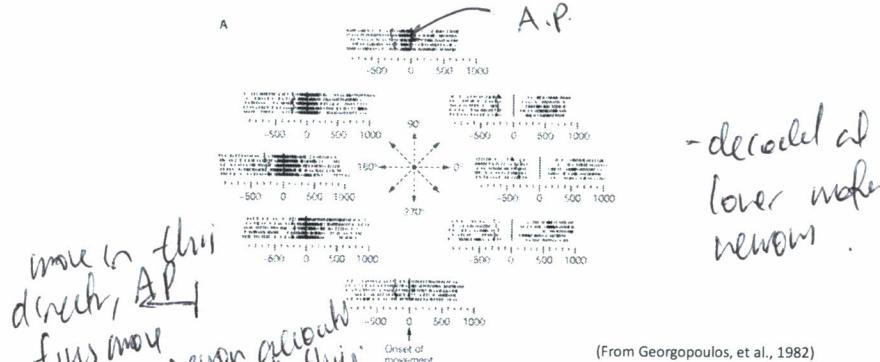
### Premotor cortices

- Coordinated movements across multiple joints
- Planning of movements
- Send projections to primary motor cortex, as well as down corticospinal tract

many areas → number of muscles contracted & relaxed in an ordered fashion.  
Send specific signals.  
(upper motor neurons).

## Generation and Control of Voluntary Movement

- Cells in the primary motor cortex encode force
  - Direction and amplitude of simple movements across single joints

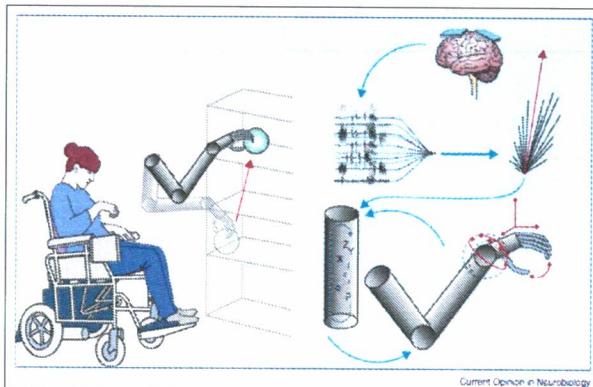


- Sites controlling individual muscles are distributed
  - Corticospinal axons (from upper motor neurons) diverge and terminate onto motor neurons innervating different muscles

## Generation and Control of Voluntary Movement

### • Prosthetics

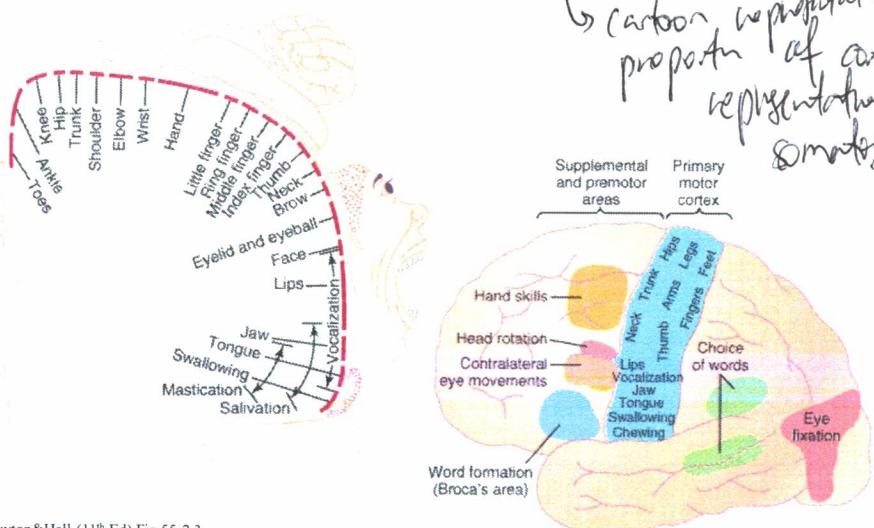
- Multielectrode array implanted in motor cortex
- Translate single unit activity into movement commands
- Integrate with robotic position feedback and task constraints



(Georgopoulos and Carpenter, 2014; figure and legend from Courtine et al., 2013)

## Motor Cortex Homunculus

↳ cartoon representation of proportion of cortical representation of somatotopy.

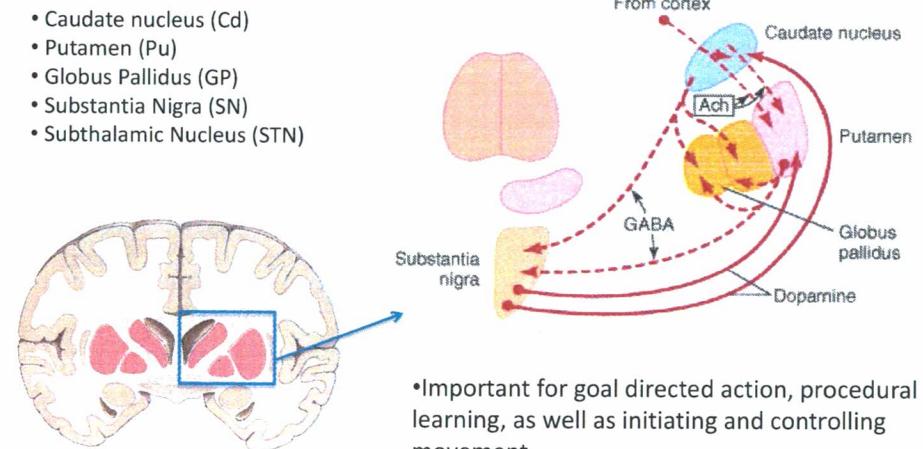


Guyton&Hall (11<sup>th</sup> Ed) Fig 55-2,3

10

## Basal Ganglia

- Caudate nucleus (Cd)
- Putamen (Pu)
- Globus Pallidus (GP)
- Substantia Nigra (SN)
- Subthalamic Nucleus (STN)

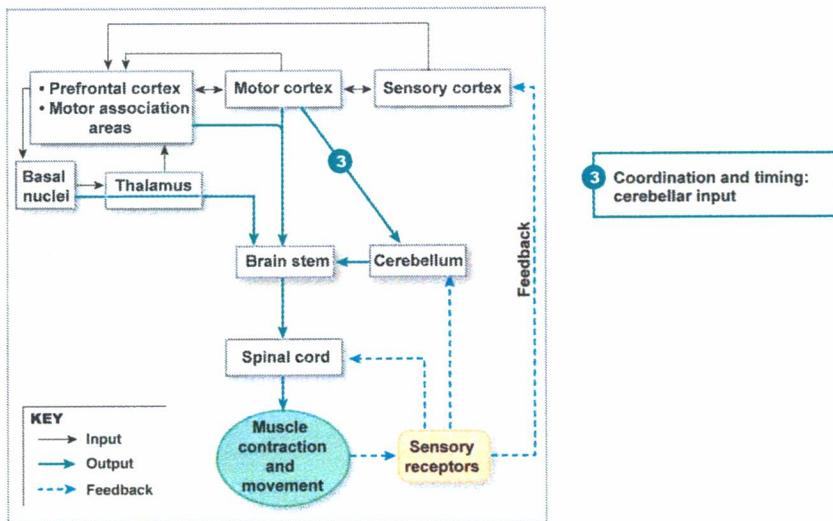


Silverthorn (5<sup>th</sup> Ed) Fig 9-11

Guyton&Hall (11<sup>th</sup> Ed) Fig 56-14

12

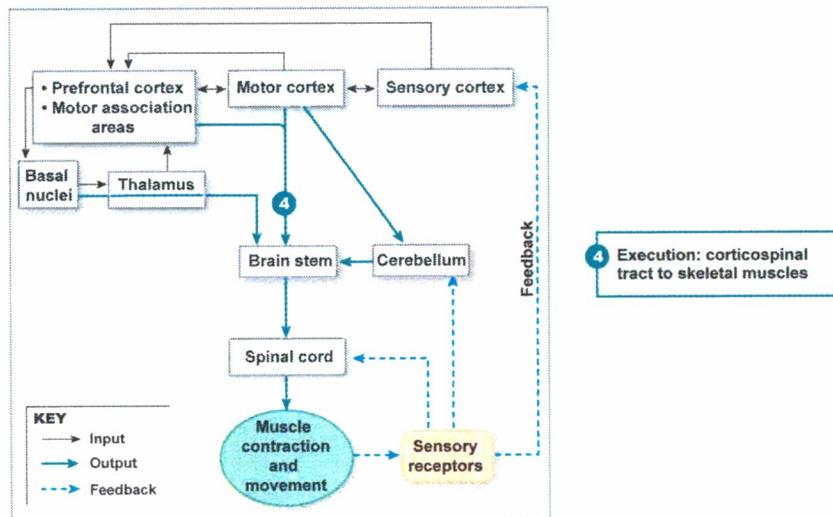
## Generation and Control of Voluntary Movement



Silverthorn (5<sup>th</sup> Ed) Fig 13-11

14

## Generation and Control of Voluntary Movement



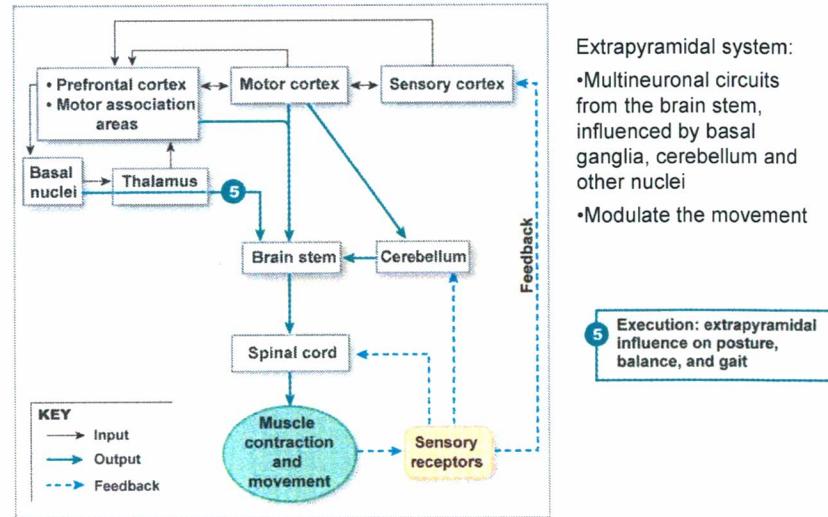
Silverthorn (5<sup>th</sup> Ed) Fig 13-11

## Cerebellum

*monitors, periphery, fuelbrain*

- The cerebellum controls but does not initiate movement
- Regulates sequence of movements
- Adjusts and corrects motor activity
- Receives input from and sends output to cortex

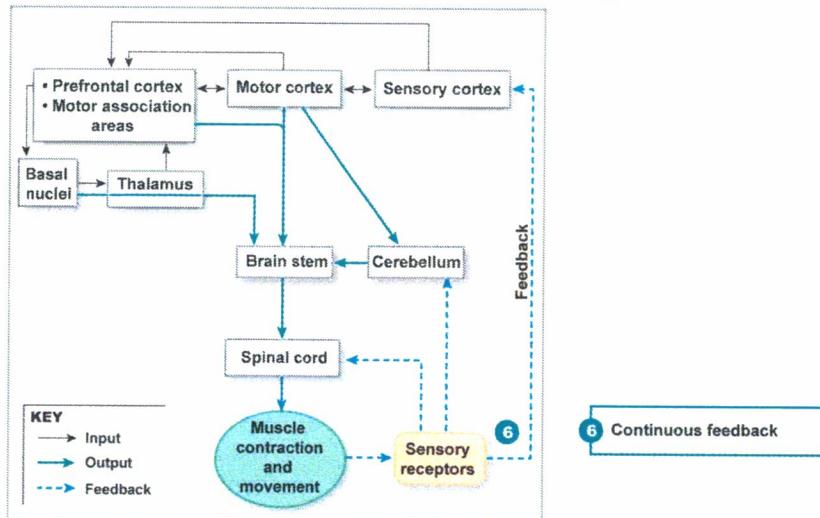
## Generation and Control of Voluntary Movement



Silverthorn (5<sup>th</sup> Ed) Fig 13-11

**Extrapyramidal system:**  
 • Multineuronal circuits from the brain stem, influenced by basal ganglia, cerebellum and other nuclei  
 • Modulate the movement

## Generation and Control of Voluntary Movement



## Disease States

### Myasthenia Gravis

- autoimmune disease
- antibodies to nAChRs
- can affect all voluntary muscle
- early symptoms include weakness of extraocular muscles
- untreated - Myasthenia Crisis - respiratory failure
- neostigmine - blocks AChE (blocks ACh)
- prednisone/cyclosporine - immunosuppressives

removal nAChRs, compromises ability to contract.  
- cannot move eye properly.  
removal in NMJ, easier to contract

## Disease States

### Malignant hyperthermia

hypertension, heat up

- rare, often familial disease
- triggered by anaesthesia
- SR Ca release channels are opened by halothane
- simultaneous release of Ca in all muscles causes contracture and raised temperature
- untreated - death through respiratory failure
- dantrolene - blocks SR Ca release valuable treatment
- caused by mutations in the SR Ca release channel

blocks RyR2 receptors, allow relaxation  
DCH.

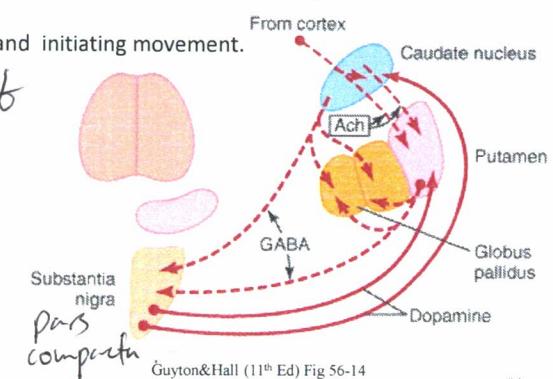
### PARKINSON'S DISEASE

- Degeneration of SNC that release dopamine onto Cd/Pu.
- Characterised by:
  1. Muscular rigidity
  2. Involuntary tremor at rest
  3. Akinesia: difficulty in planning and initiating movement.

Stable dopamine.

decreases motivation to move.

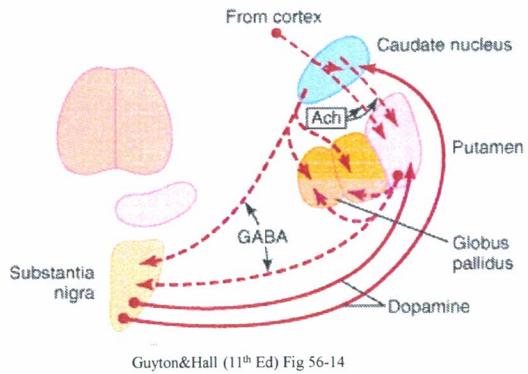
Silverthorn (5<sup>th</sup> Ed) Fig 9-11



## Basal Ganglia Dysfunction

### HUNTINGTON'S DISEASE

- Severe distortional movements of the entire body.
- Hereditary disorder: Degeneration of GABA secreting neurons in Cd/Pu.



Guyton&Hall (11<sup>th</sup> Ed) Fig 56-14

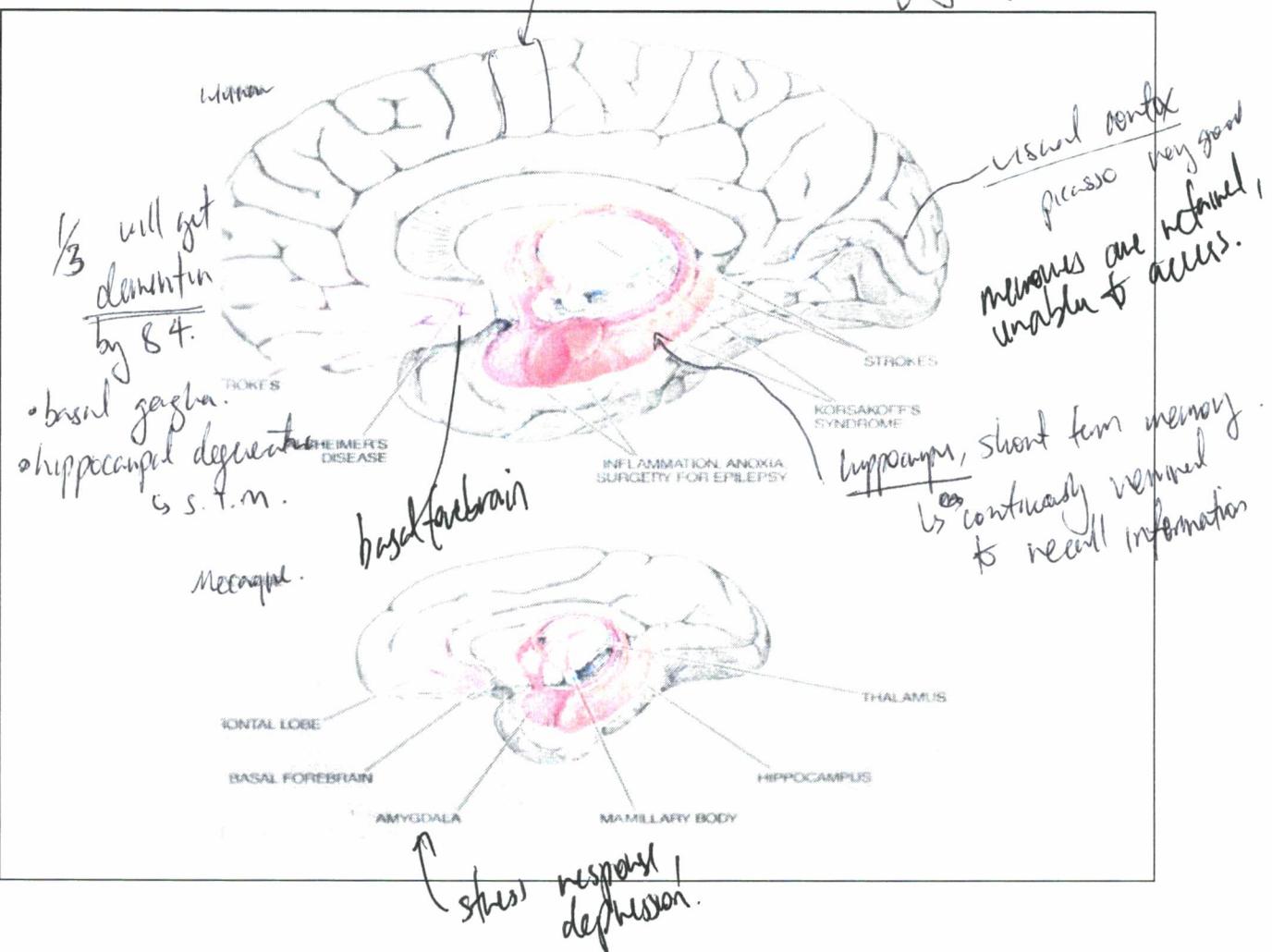
Cortex, basal ganglia

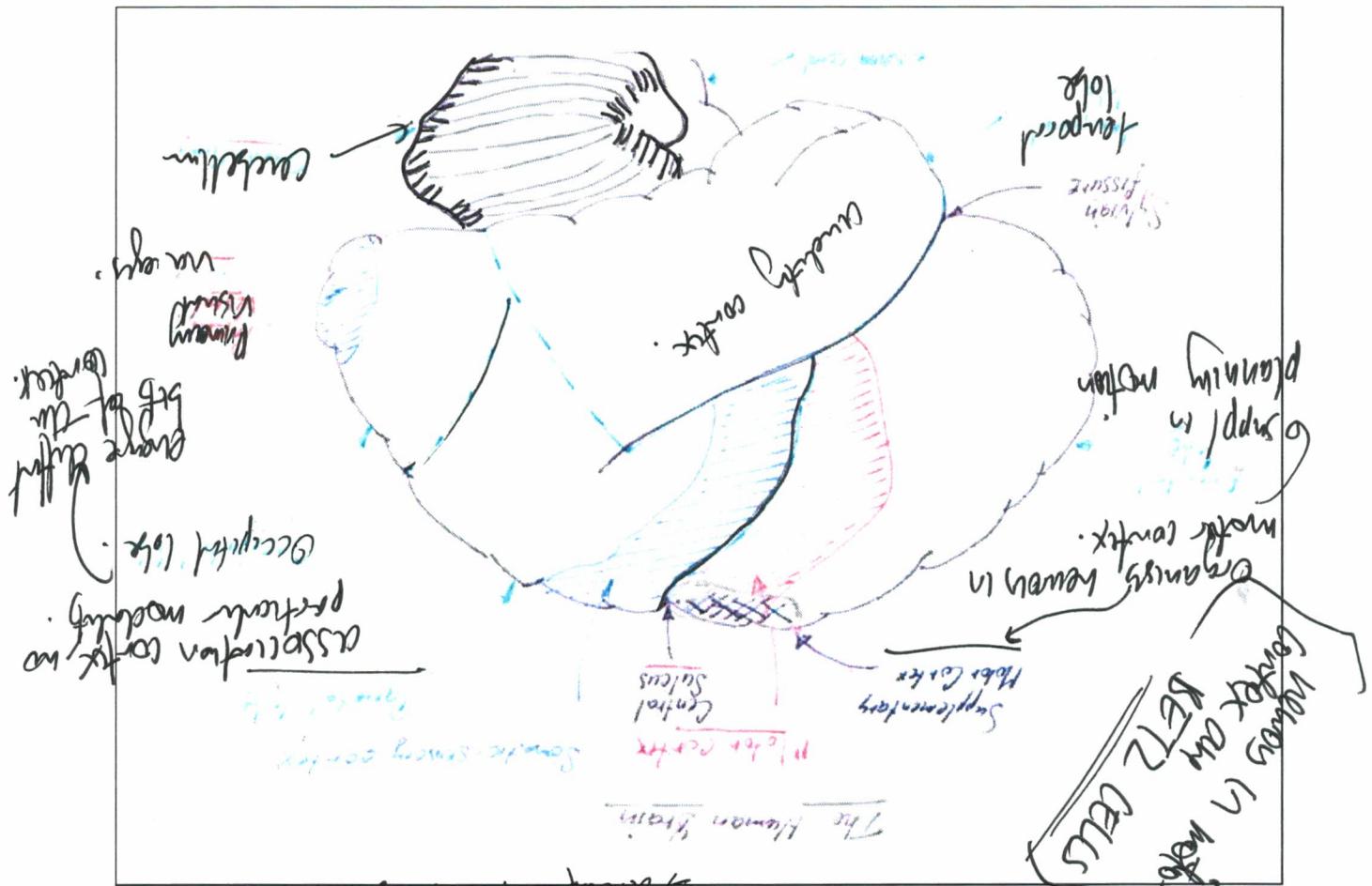
limb movement  
movement surpassing circuit damaged.  
movement inhibitory circuit damages later.

# Lecture 1

## The Brain

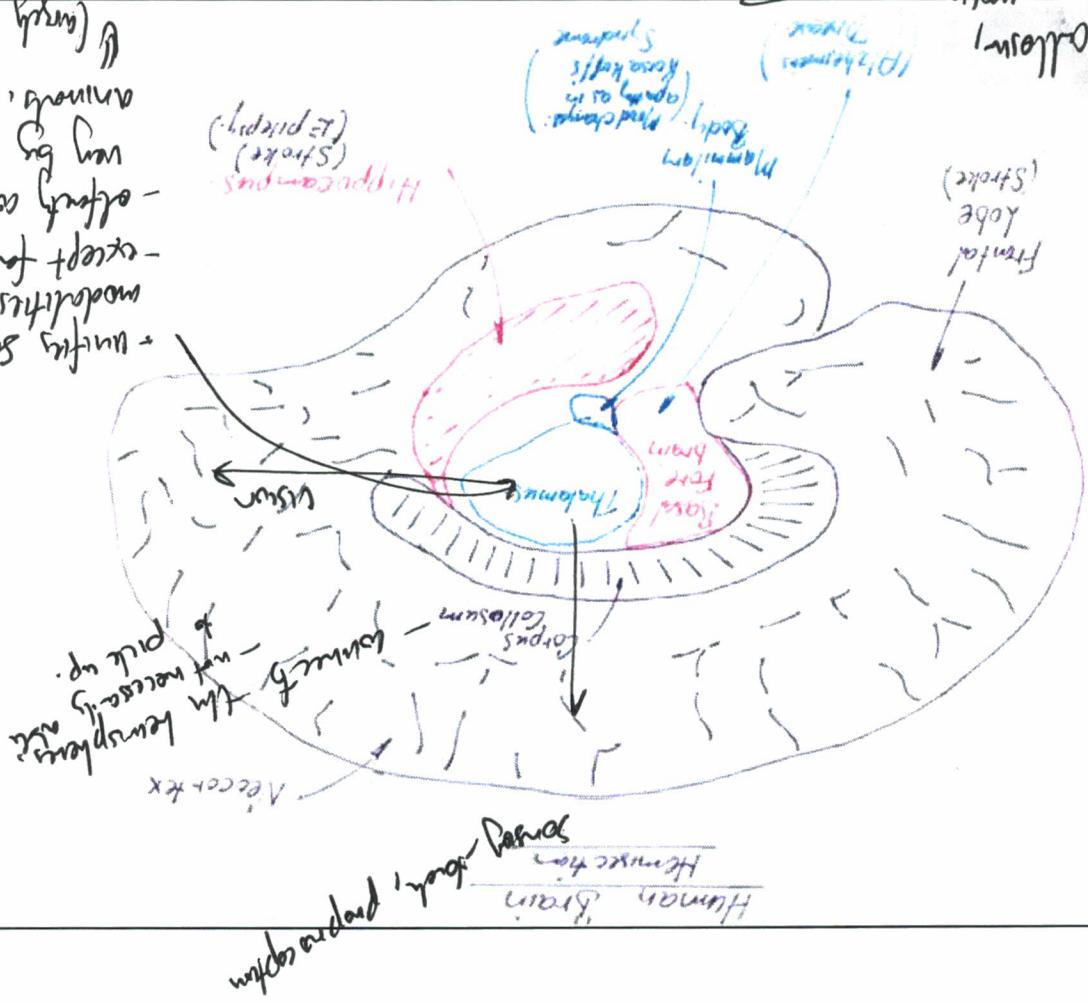
Motor cortex  
 Solitary  
 strokes causes dysarthria  
 & paroxysms, incontinence & more.  
 very long memory ↗  
 very long cortex.

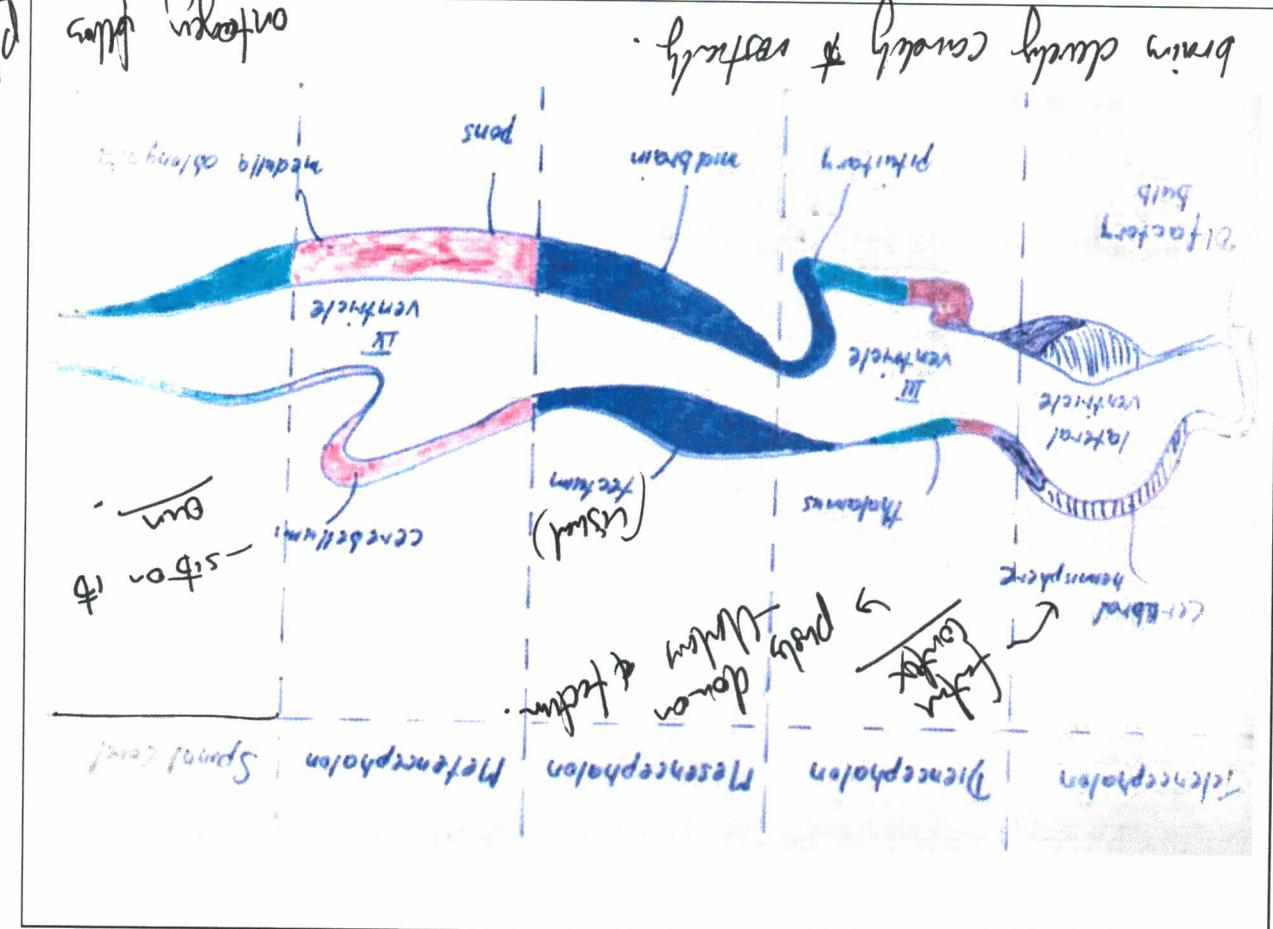
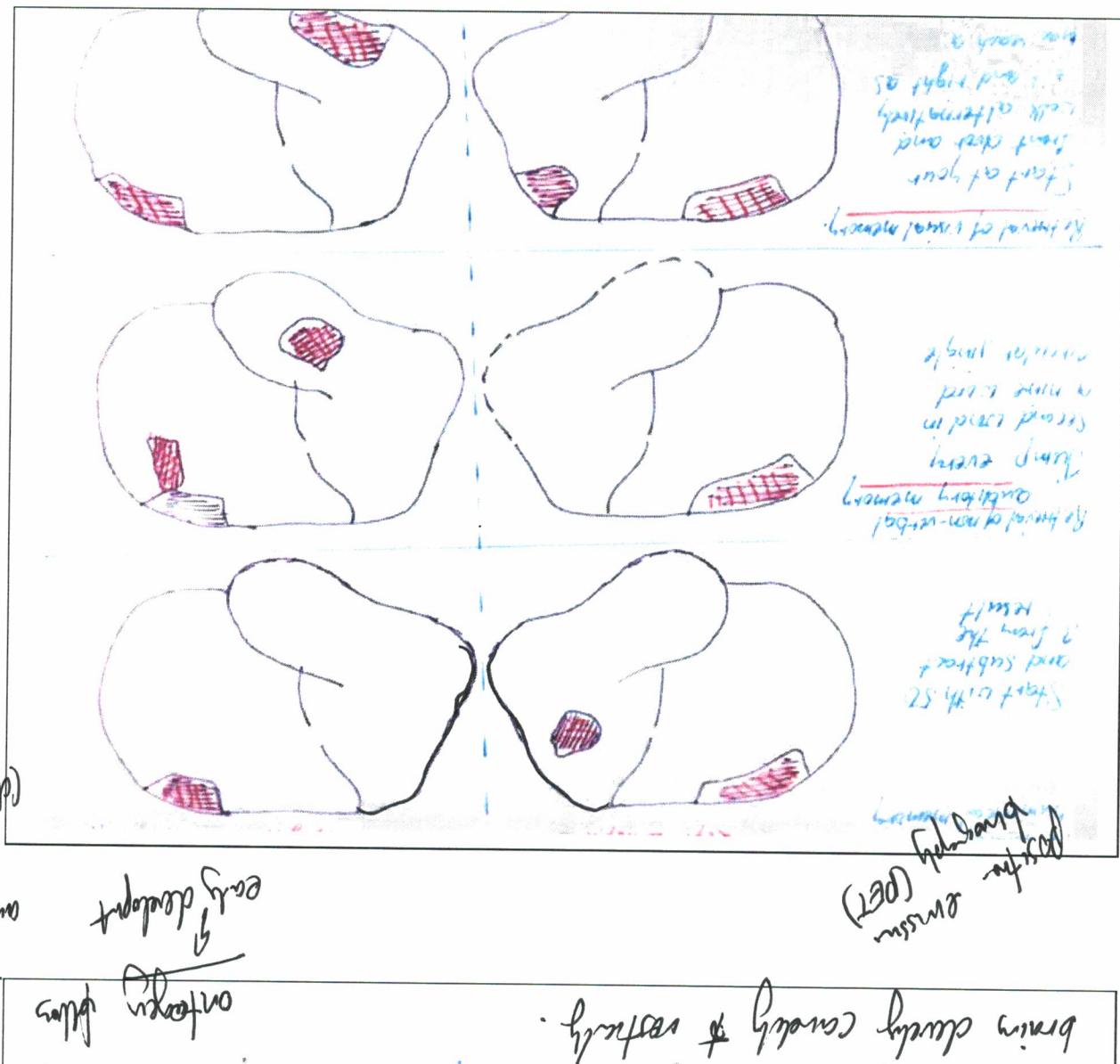


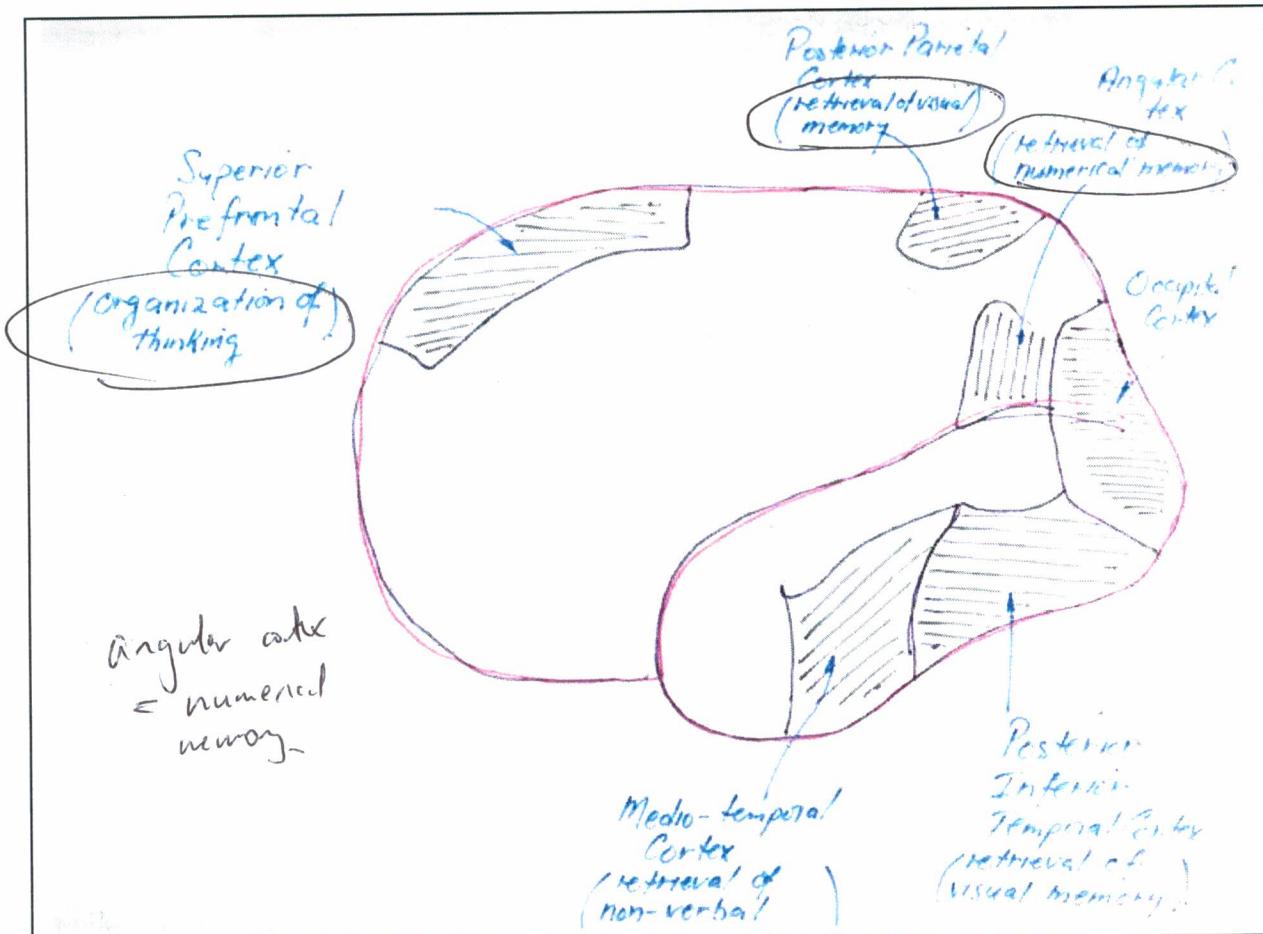


parent, sibling, brother → initially soft hair  $\hookrightarrow$  loss of plausibility as well.  $\Rightarrow$  different strokes in different hair.

- layers (phytopl) 
- granular
- meso vs big lumps
- soft/friable surface
- except for bottom
- moderate infiltration
- poor infiltration

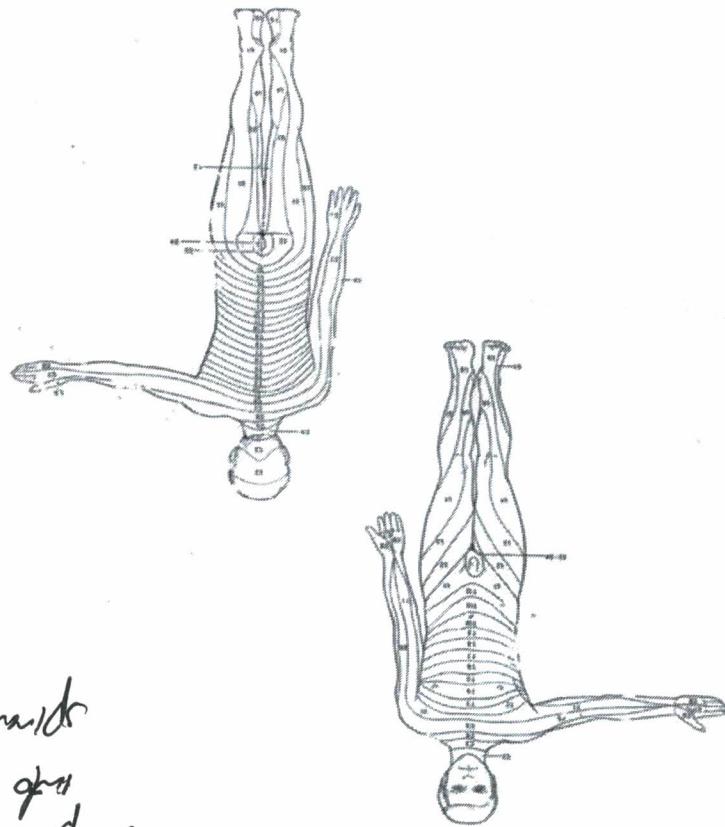
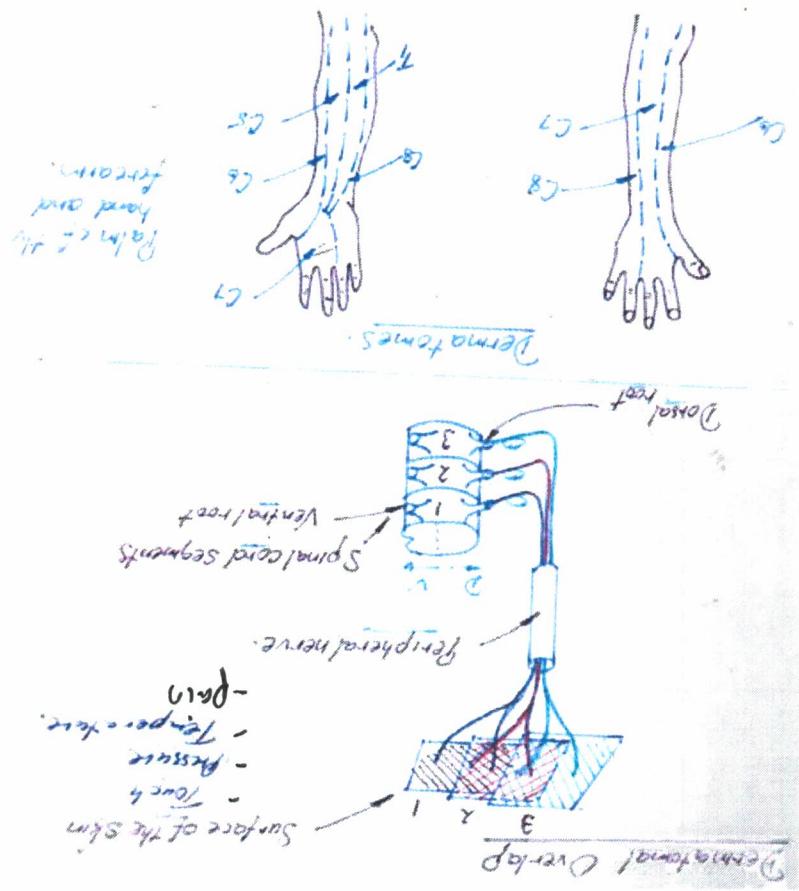




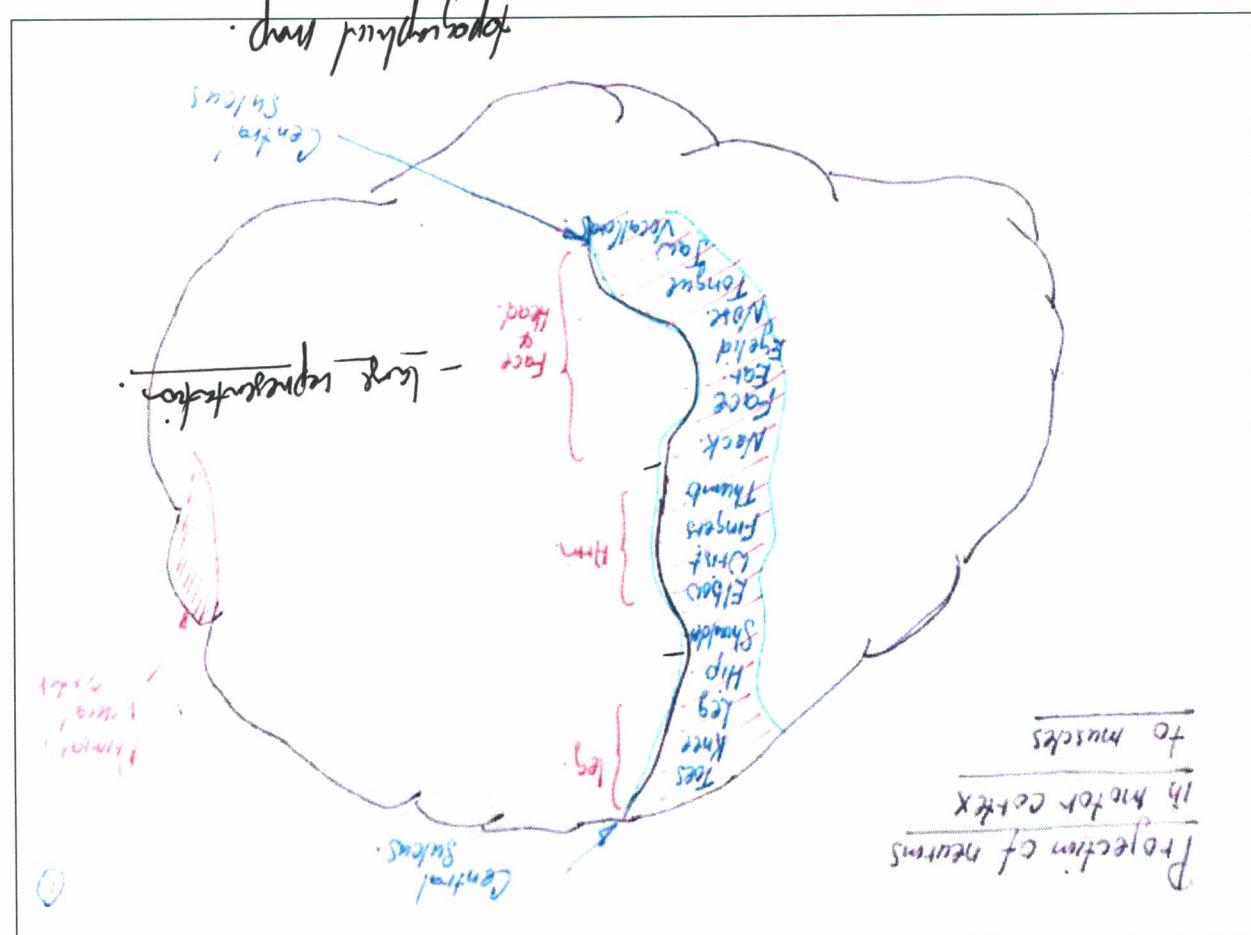
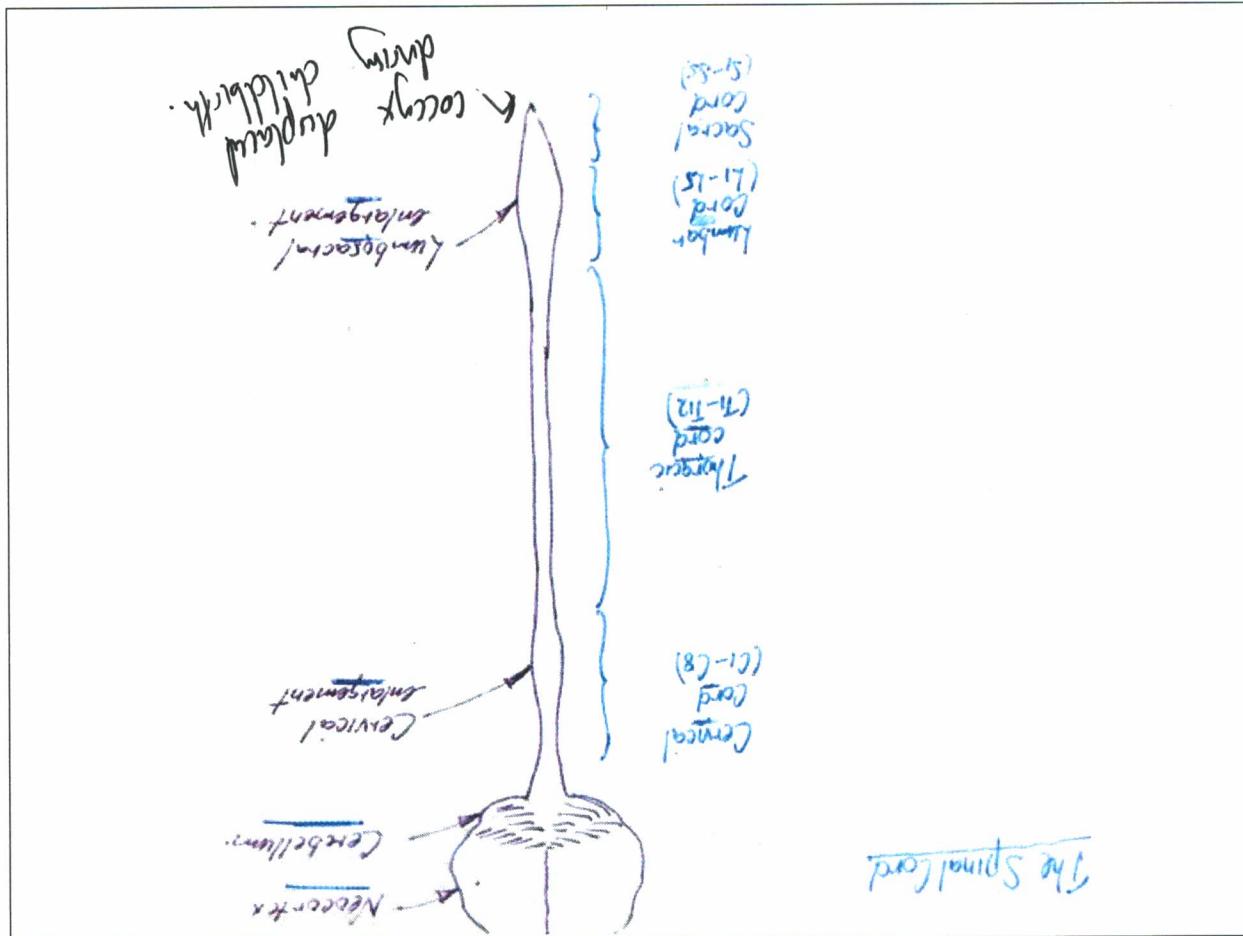


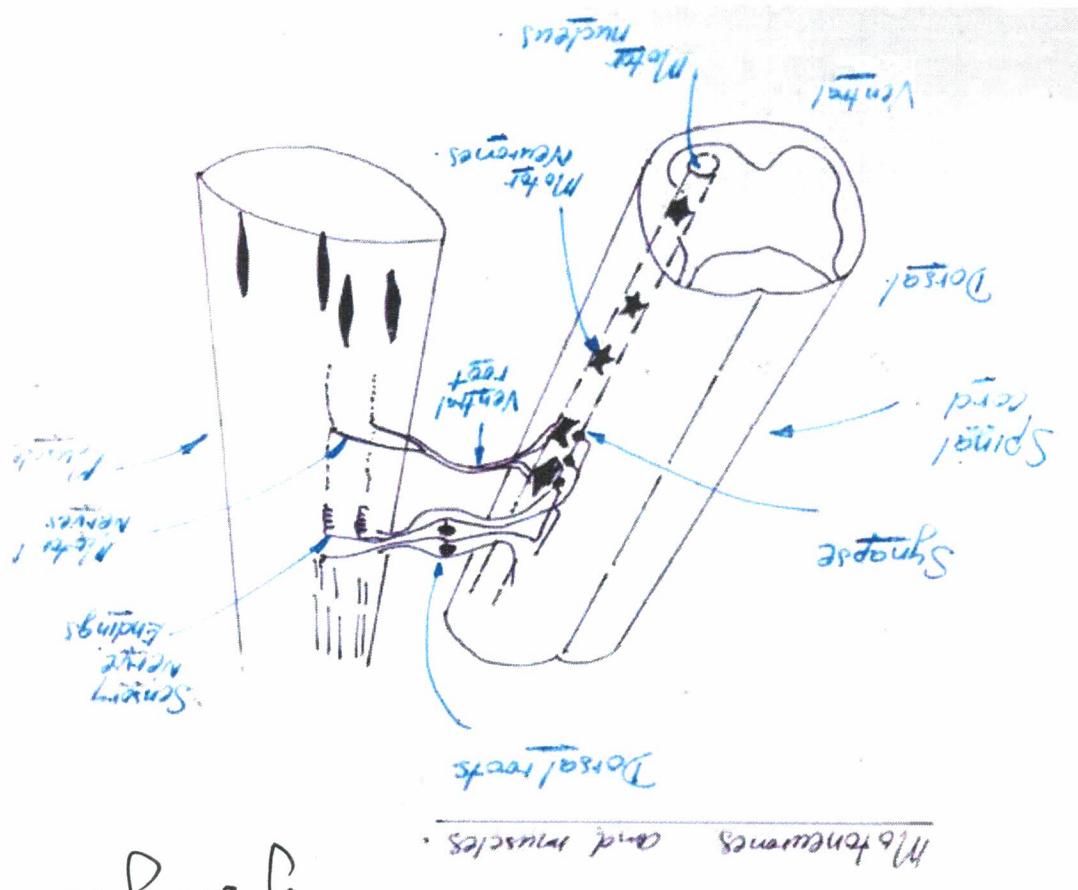
## Lecture 2

# Sensory & Motor System

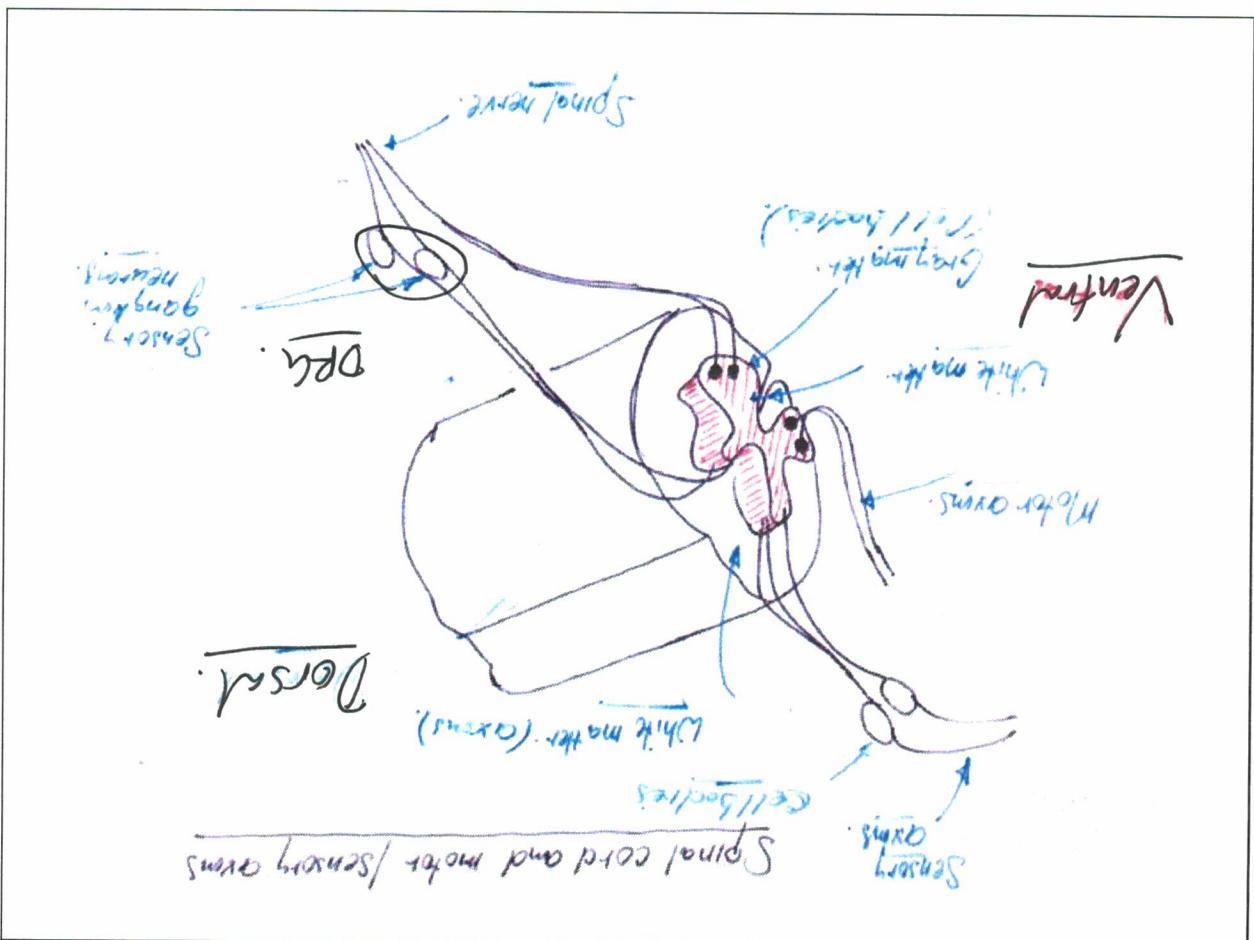


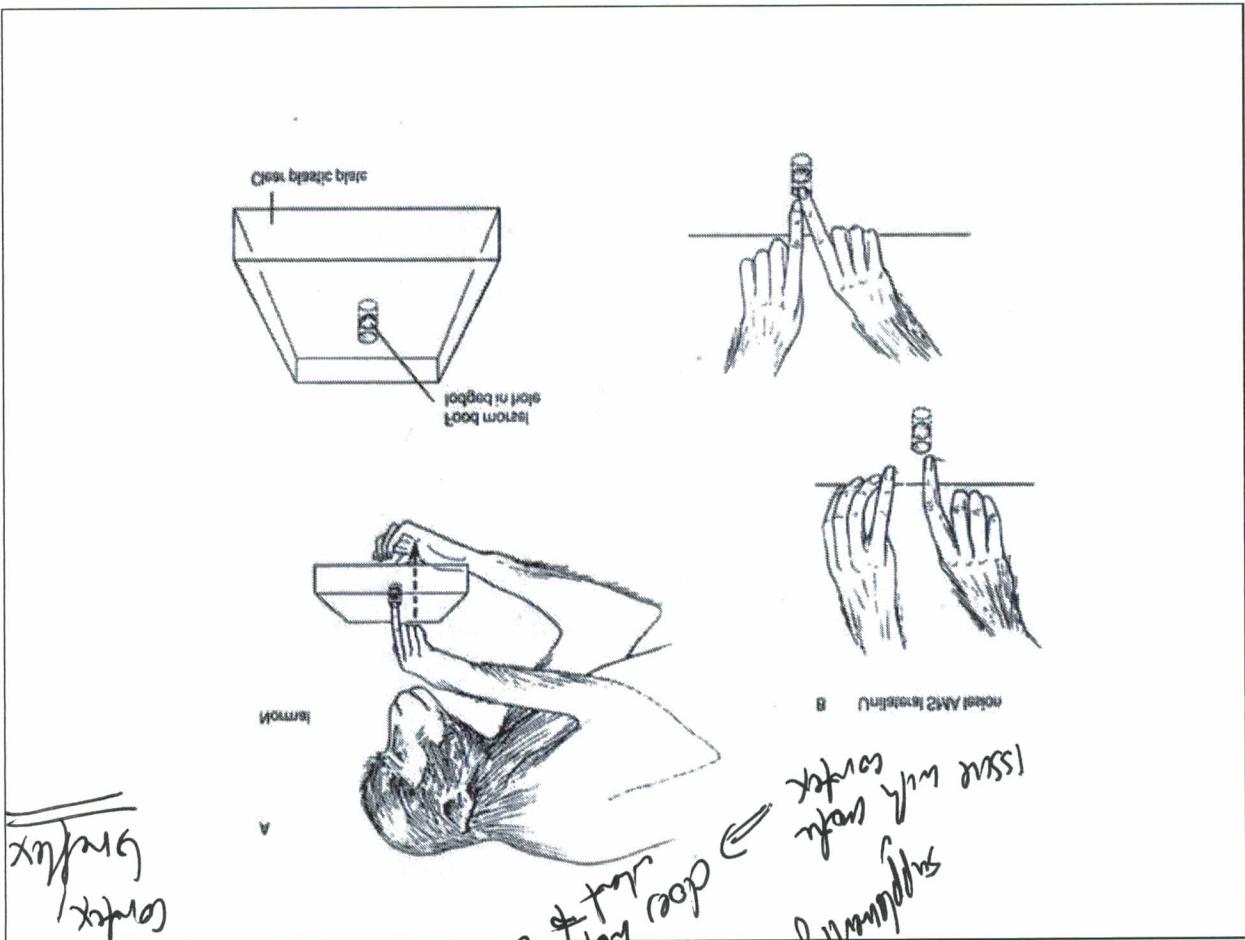
part of the system



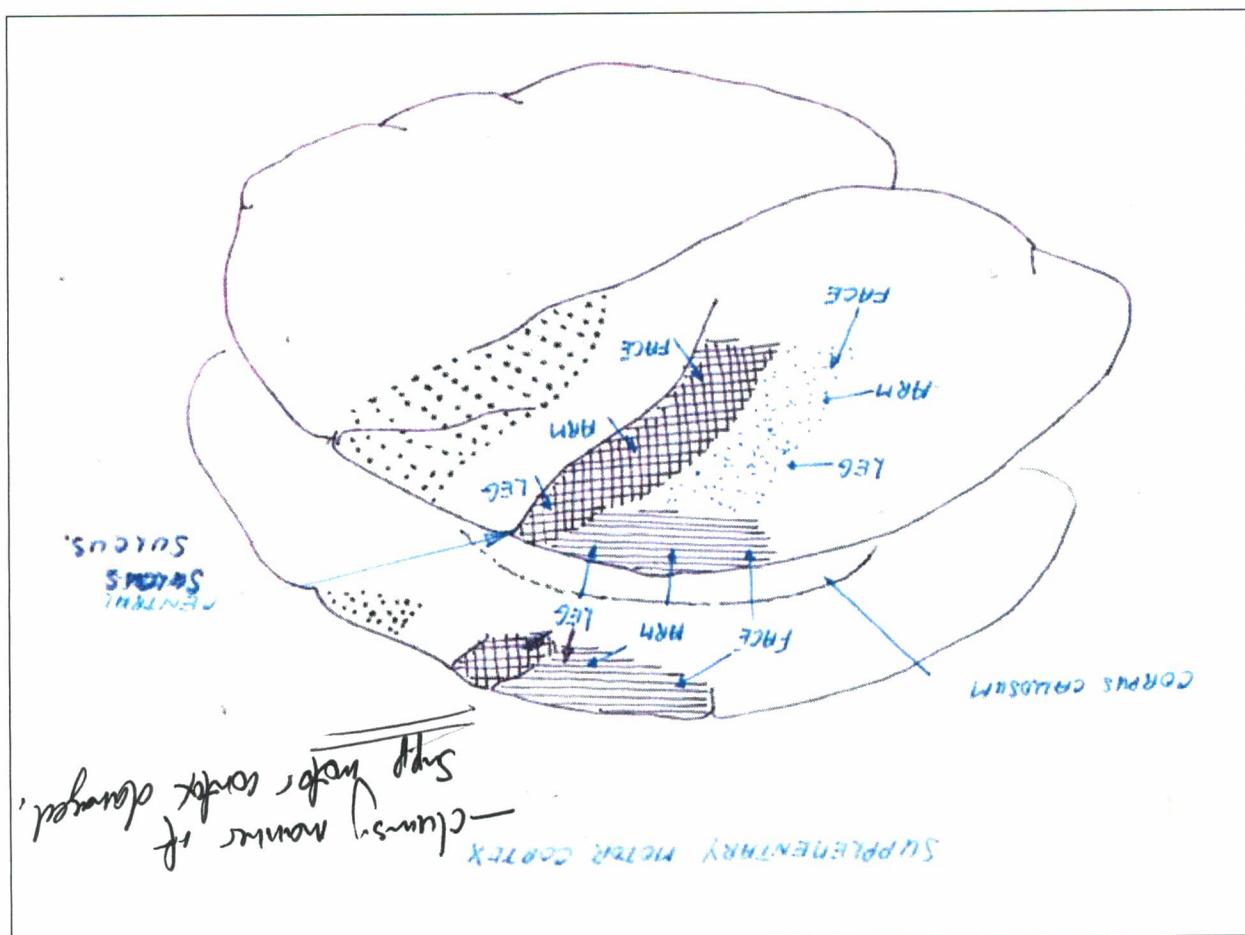


Spinal synapses near cord  
Interneurons also involved





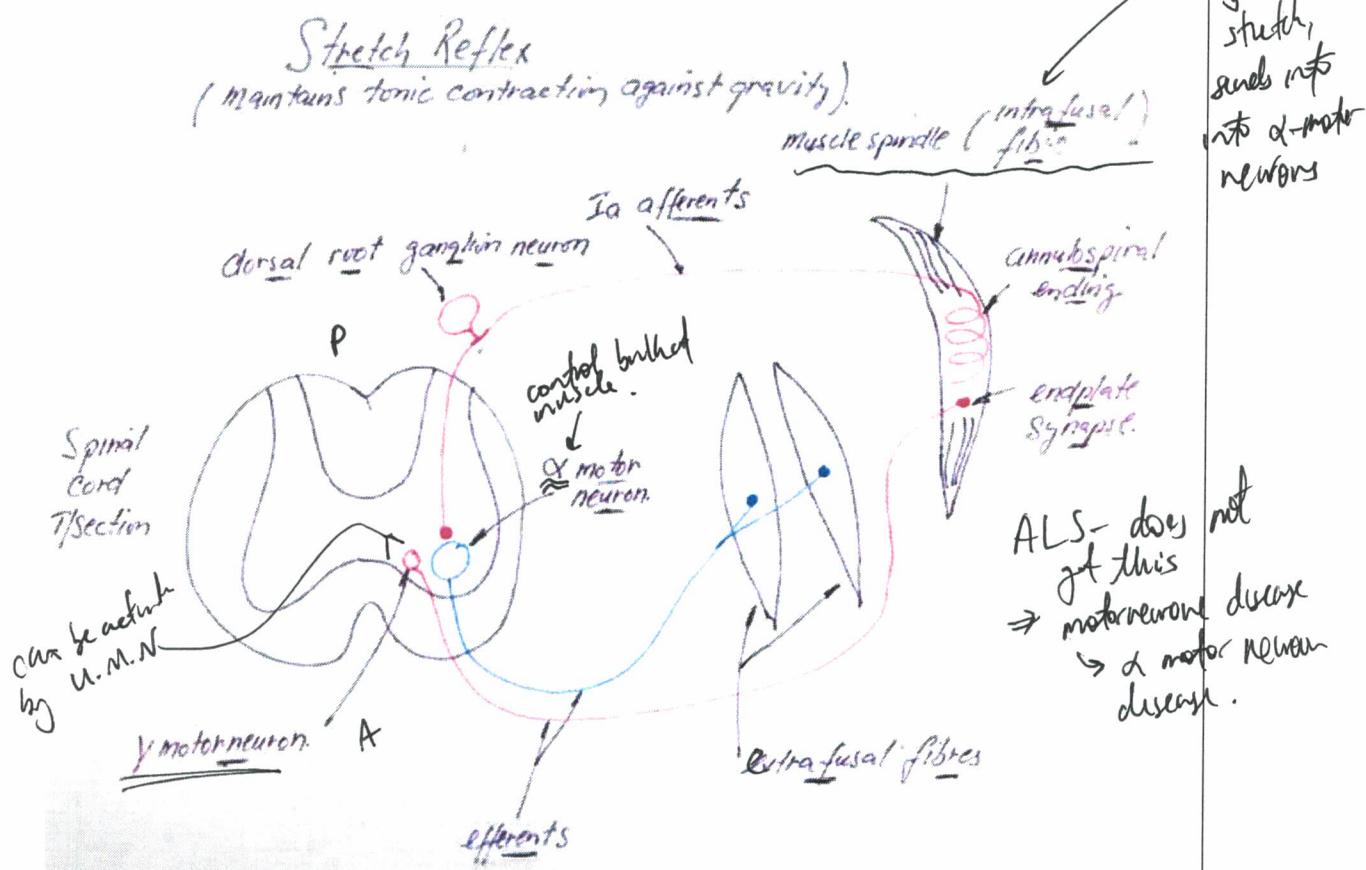
Issue with sharp tools

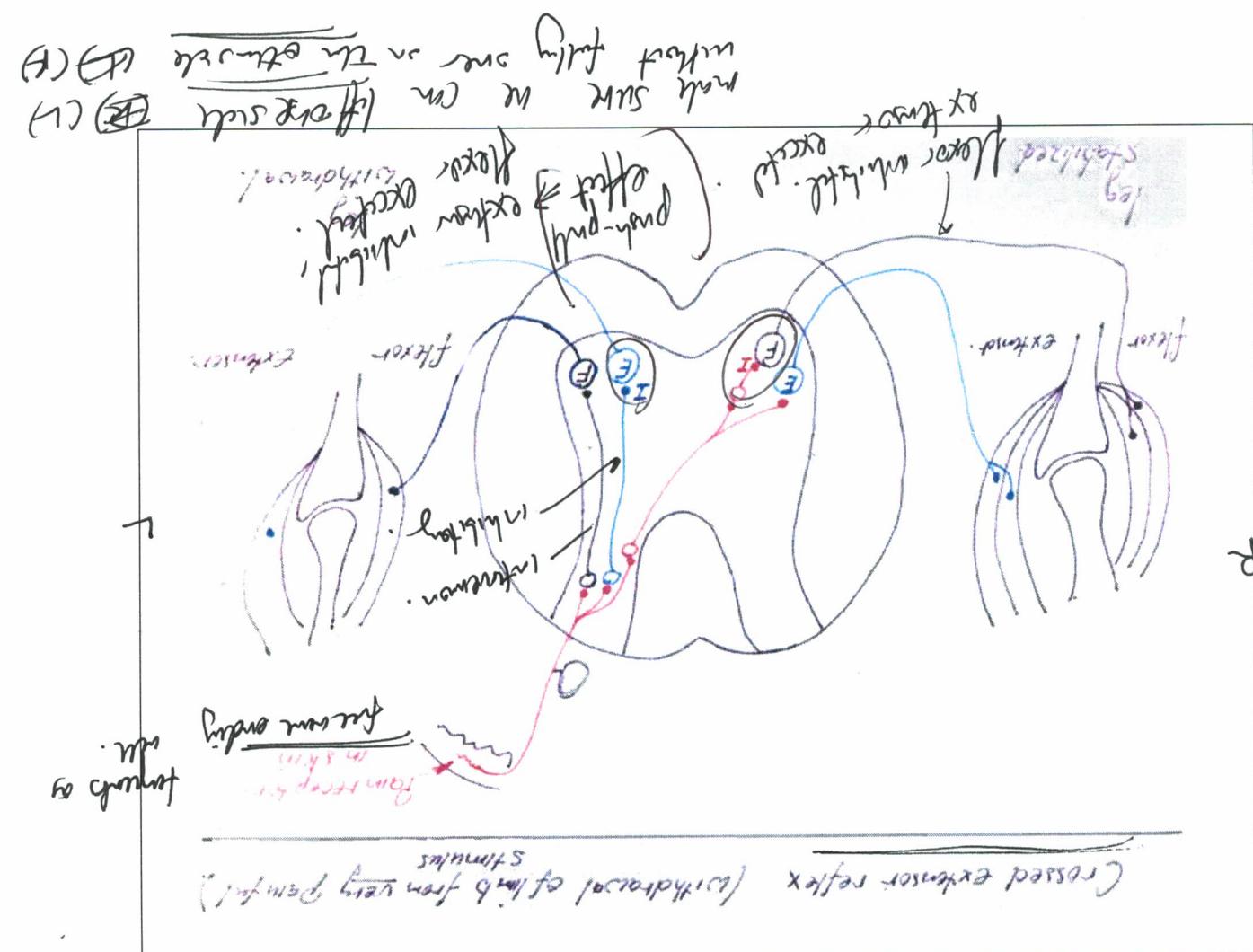
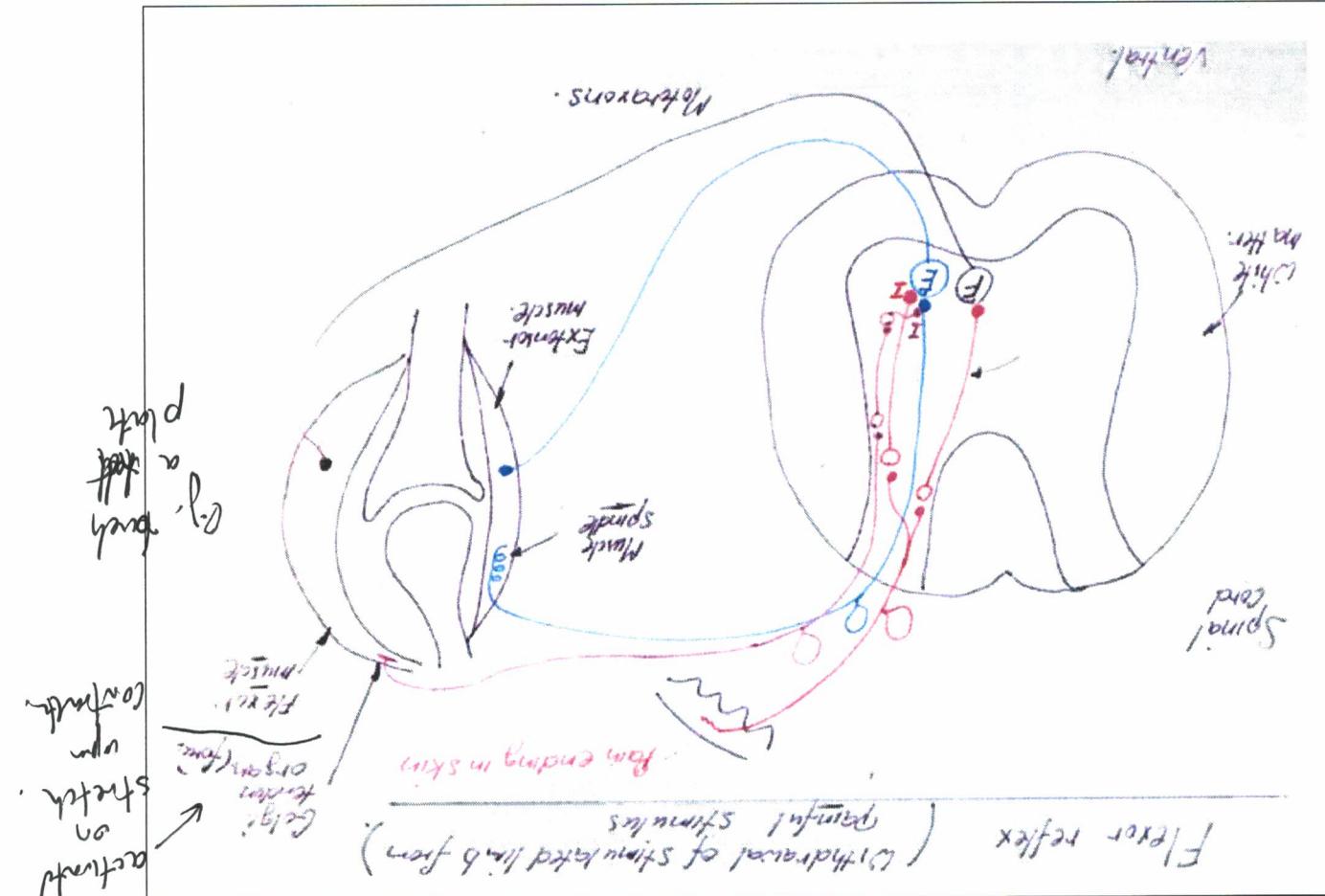


# Lectures 3

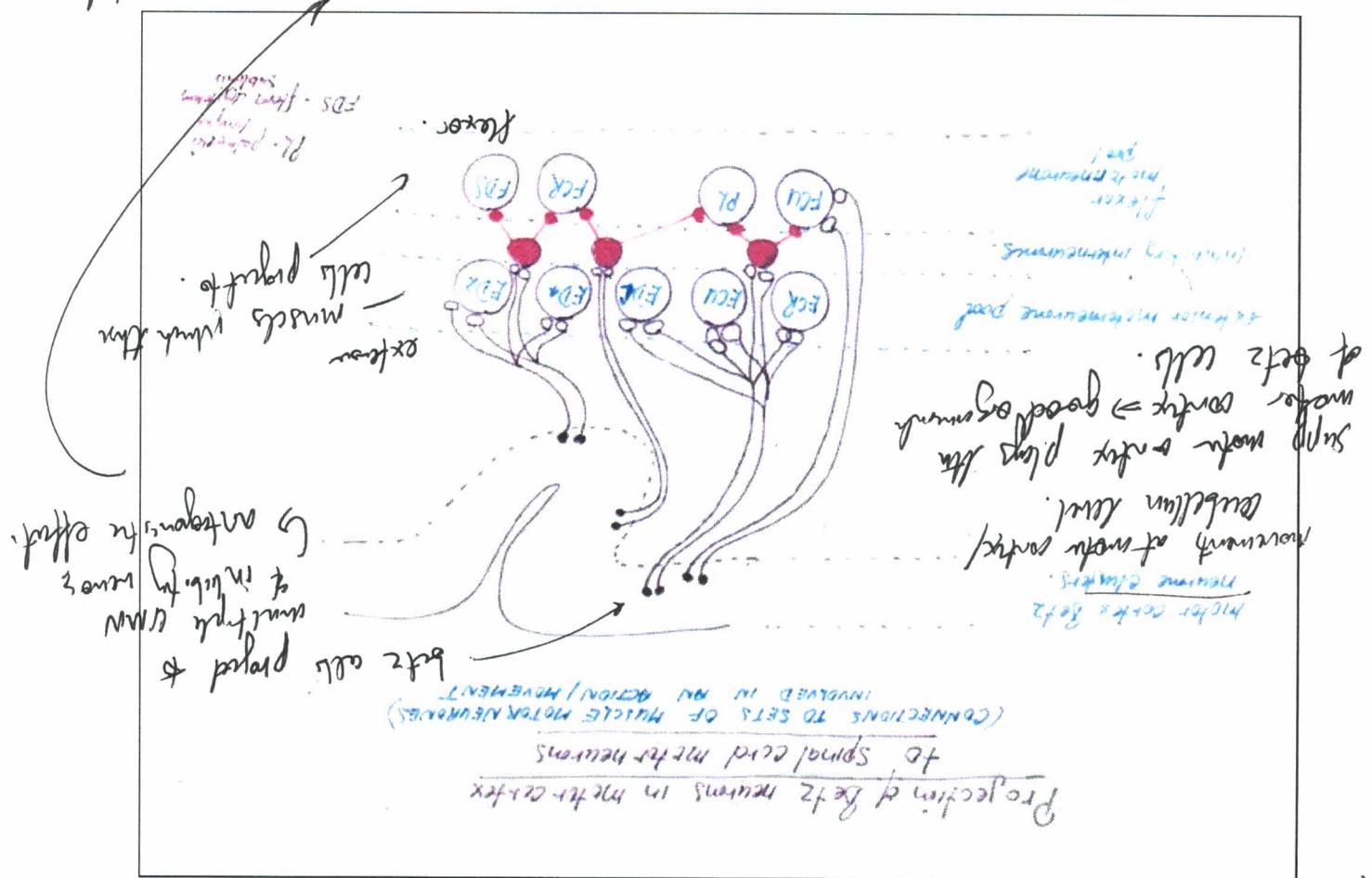
## Motor Reflexes

contractile receptors → contract extrafusal fibres,  
very few intramuscular muscle.  
→ intramuscular muscle is like a spring

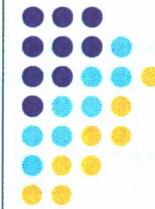
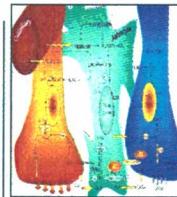




With exterior insulation, there is insulation.



# Report Writing



## Language & style

- Write from reader's point of view
- Present information in a logical order for the reader
  - Use section headings
  - Main points should be obvious
  - Provide conclusions
- The quality of your written communication will influence your reader's understanding



## What is a report?

- Form of professional documentation
- Designed so readers can readily extract information
- Describes experimental work in sufficient detail for it to be repeated and verified by others
- Interprets/draws conclusions from experimental data
- Places conclusions in context of related work in the field



## Language & Style cont.

- Simplicity and clarity: easy to follow your thinking
  - Use short, precise, concise sentences
- Avoid words/phrases with a meaning that could be interpretative
  - Considerable, rather large, lots...
- Use objective language

**Objective:** Blood pressure and pulse were measured at 5 min intervals for 30 min.

**Subjective:** We measured our partner's blood pressure and pulse every 5 min for 30 min.

- Use past tense and passive voice

**Passive:** Acetone (10 mL) was added to the mixture drop-wise.

**Active:** I added 10 mL of acetone to the mixture, one drop at a time.



## When writing

- Use appropriate scientific terminology
- Define terms when used
- Write acronyms/abbreviations out in full 1<sup>st</sup> time
  - Both in report text and in any legends
  - No need to define universally understood abbreviations. E.g., units of measurement

The volume of air entering or leaving the lungs during a single breath, the tidal volume (TV), under resting conditions is 500 mL.

## Report is 16% of Unit assessment

Compulsory exercise – you must submit or AF

## PHSI2005 report will be on:

- **Muscle Practical**
- Force–Length Relationship: Exp. 3
- Sarcomere length (Laser diffraction): Exp. 6
- **I.e., macro & micro aspects of muscle physiology and mechanism**

## Specific structure

- Title
- Abstract
- Introduction
  - Hypotheses
  - Aims
- Methods
- Results + Figures and Tables
- Discussion
  - Conclusions
- References

## Where to begin...

- Title

Effect of dietary trans fatty acids on high-density and low-density lipoprotein cholesterol levels in healthy human subjects

## Introduction

- Introduces the key theoretical concepts
- Provides a brief background
  - Figure(s) can be helpful!
  - Reference published material

## Abstract

- Summarises the whole report
- Concisely describes the
  - Rationale for experiments
  - Results (including quantitative values)
  - Main conclusions
- 200 words maximum
- Check out Abstracts online
  - E.g., American Journal of Physiology – Cell Physiology

## Conclusion

## Hypotheses and Aims

- Null and predicted one-tailed hypotheses for:
  - Relationship between active force and muscle length
  - Relationship between passive force and muscle length
- State aims of Exp. 3 & 6
- Make sure hypotheses and aims are correct
  - Avoids problems down the track!

## Methods

- Concise, well-organised summary of experiments. **Include:**
  - The source of the biological material and how prepared
  - Methods used, including equipment
  - How data was worked up. E.g., how you measured passive and active forces from the traces you generated.
  - Write in narrative form. Not as bullet points
  - Use past tense
  - Use scientific/technical terms correctly
- No trivial or unnecessary details



## Tables and Figures

- Table of raw data (values of independent & dependent variables)
- Graph(s) of data (You may wish to include one or more stimulus traces)
- Titles
  - Single descriptive sentence
  - Include the dependent and independent variables
- Legends
  - Sufficient to understand figure/table without text
  - Include sample size, explain symbols
  - Don't include data interpretation
- **Don't lump together before Results text**
  - Place appropriately for reader



## Results

- Tells reader what was observed experimentally in logical order
- **Describe data briefly**
  - Baseline values
  - Key changes
- Closely linked to graphs and tables
  - Don't simply regurgitate values from tables/graphs
- Write in past tense
- Don't interpret results
- Don't repeat descriptions of methods

During the rest period there was no change in mean heart rate (HR). Mean HR peaked after 5 min of exercise (Fig. 1).



## Tables and Figures cont.

- Figure/title/legend (adapted) from a published source usually not entirely appropriate
  - Change each of these for your specific purposes
  - Include source as reference in legend and reference list



## Tables and Figures

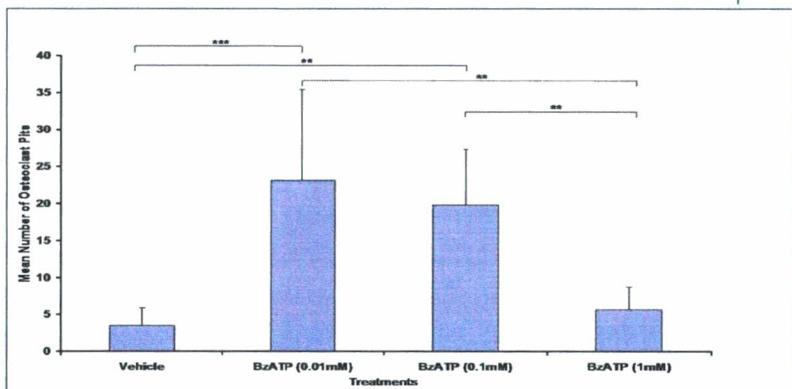


Figure 7. Quantification of human osteoclast activity treated with BzATP. Error bars represent standard error of the mean. \*\*\* Significantly different ( $p=0.0067$ ), \*\* Significantly different ( $p=0.0108$ ) (Modified from Barron et al, 2008)

## Discussion cont.

- Don't be vague in your arguments!
  - "Lack of precision in measurement" – what measurement? Why imprecise?
  - "The results were as expected" – what was expected? Why?
  - "The plot is sort of linear" – is it or isn't it?

## Discussion

- Link results to hypotheses and underpinning physiological/molecular mechanisms
- Focus on mechanisms/physiology delivered in your lectures, prac, your textbooks/other textbooks.
- Are your results as expected?
  - Do data support the hypotheses?
- Interpret your results
  - Compare your results to expected
  - Explain mechanisms underlying them
- Don't simply restate Results

## Conclusions

- Briefly summarises Discussion: 2-3 sentences
- Concise and logical
- Begin with most important points and work down
- Don't introduce new material

## References

- Original articles/reviews, textbooks, lecture and prac notes
- Use a single standard referencing system
  - Harvard format *only*
  - No web links! (except maybe for a web picture)
- References in text must match those in reference list and vice-versa



## Common Past Problems cont.

- Cutting and pasting without understanding
  - Failure to discriminate between relevant and irrelevant information
  - Unnecessary repetition of information in slightly different words
  - Loss of logical flow and linkage of related ideas



## Common Past Problems

- Not linking macro & micro aspects
- Not comparing results to published values
- Failing to introduce and discuss all relevant molecular mechanisms and physiological aspects
- Lack of appreciation of protocol details
- Failure to summarise adequately in Abstract and Conclusions
- Figures and Tables missing key elements and legends lacking details



## Play close attention to:

- Logical flow and linking of ideas
- Using concise, precise, short sentences
  - Don't make vague, general statements
- Correct spelling and punctuation
- Correct grammar
  - Sentence structure, verb-subject agreement, verb tenses
- Appropriate use of vocabulary, especially scientific terms
- Clear separation of paragraphs
- Staying within the word limit

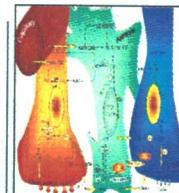


## Optional Draft Report



- Formative and useful!
- Focus on **Abstract, Intro, Results, Figures and Tables**
- Submit as hard copy: SLO, Tue 10<sup>th</sup> May
- Submit as electronic copy: Blackboard, 10<sup>th</sup> May
- Sections must be complete!
- Returned with comments midday Mon 16<sup>th</sup> May

## Academic dishonesty - Plagiarism/Collusion



## Final report

- Due Tue 24th May 5.00 pm (Week 12)
- Electronic copy via drop box on Blackboard
- **MUST** be a Word document
- **MUST include:**
  - First & last name, SID, email address at top of front page
  - Marking rubric
- **Serious marks will be lost if you fail to do any of these things!**



**No excuses for academic dishonesty of any kind**

- Unacceptable practice which:
  - Devalues your degree
  - Reflects badly on the University
  - Gives unethical advantage

## Collusion

- **DO NOT** give to another student:
  - Complete or near complete copy of your report
  - Or parts thereof
- What do you think they will do with your copy?
- **DO NOT** dictate for another student to copy
- **DO NOT** claim ignorance of collusion if you have done these or related things



## Avoid plagiarism!

- Use your own words
- Not other people's
- Always reference your sources
- **Just because you reference doesn't mean you haven't plagiarised!**
  - You still must use your own words!
  - Changing a few words around isn't enough!
- A *small* number of referenced quotes is OK



## Plagiarism

- Claiming other people's work as your own
- Plagiarism software used
  - Internet sources
  - Published works
  - Past and present student papers
  - Etc...



## No excuses!

- "I didn't know it was plagiarism."
- "I didn't know I was colluding."
- "I thought it was ok to do it for this assessment."
- "I thought it was ok if I cited the reference."
- "I accidentally submitted the wrong electronic copy, which was my friend's copy."
- "She asked for a copy of my report. I gave it to her. I didn't know she was going to plagiarise my work."
- "I asked for a copy. He gave it to me. It's not his fault. He never knew that I copied from it."
- "I read it out. I didn't know he was typing what I was reading."
- ***And on it goes...***



## Collusion/Plagiarism penalties



- Serious penalties apply and are often applied

- Up to 100% of report mark
- Official action by the University
- Transgressions listed on register at Sci Fac Office and Registrar's Office
- Written warnings, notations on transcripts, a mark of 0 for the Unit
- **Very lengthy process – weeks to months**
- Results remain as INC till resolved
- Affects subject selection in following semester

## Bottom line



- No excuses
- Don't do it

## Policies, information and help



- Links listed in UoS Outline in Blackboard
- This lecture
- Prac report instructions
- Ask an academic

## Report is 16% of Unit assessment



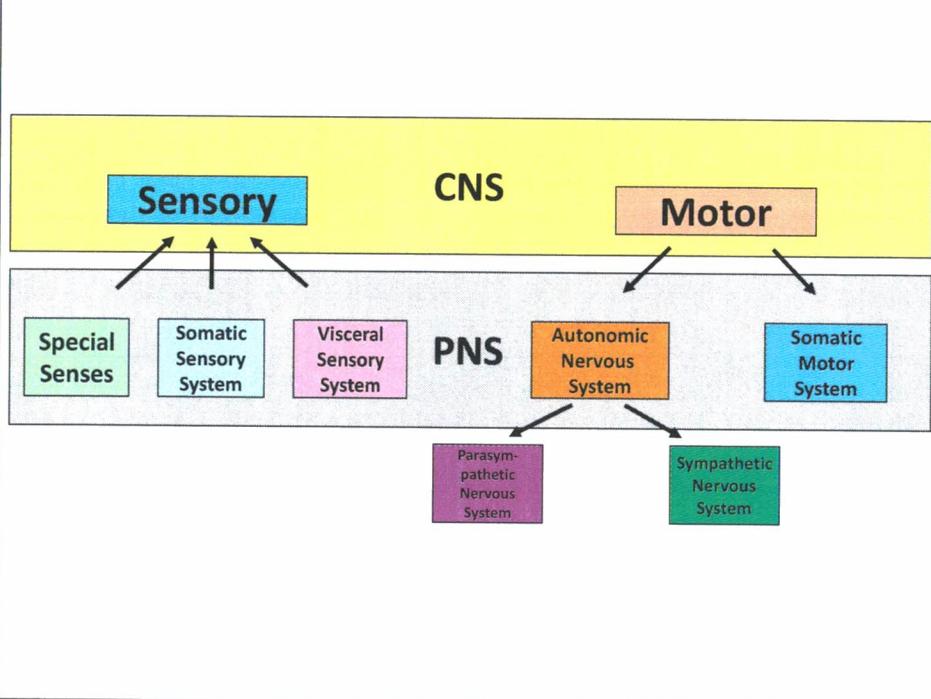
This is a rough guide of the division of marks – it may change a bit

Section	~%
Title	2
Abstract	7
Introduction with Aims and Hypotheses	22
Methods	5
Results inc. Tables and Figures	17
Discussion and Conclusions	23
References	4
Presentation, spelling, grammar, flow of ideas	20
<b>TOTAL</b>	<b>100</b>

# The Autonomic Nervous System

Dr. Atomu Sawatari  
Room N105 Anderson-Stuart  
atomu@medsci.usyd.edu.au

Refs: Dee Unglaub Silverthorn 4<sup>th</sup> edition. Most of chapter 11.  
Plus: section on the eye in chapter 10



## The Autonomic Nervous System

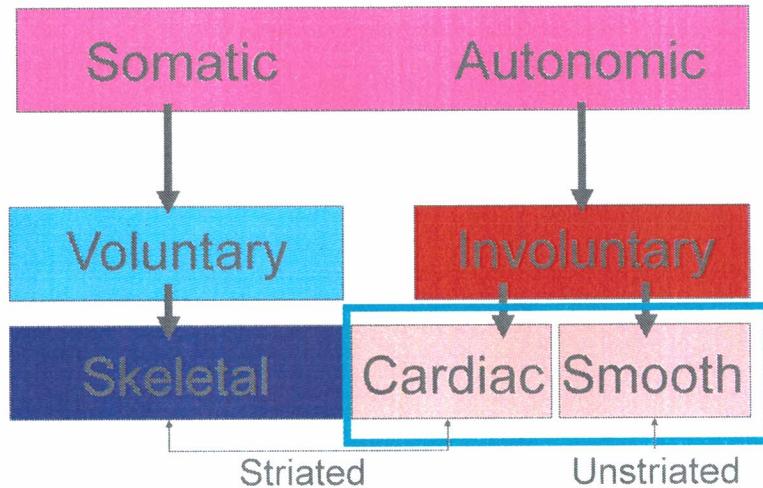
- Where does the ANS fit into the rest of nervous system?
- Structure of the ANS, comparison to somatic nervous system
- Sympathetic and Parasympathetic divisions: similarities and differences in anatomy, function, transmitters and receptors
- Clinically important agonists and antagonists (e.g., atropine and salbutamol)
- The adrenal gland: a special case
- Dual innervation and sympathetic vs. parasympathetic dominance: relevance to “fight or flight” vs. “rest and digest” and effect on major organ systems
- Hierarchical control of ANS
- Example of an autonomic circuit and reflexes: pupillary light reflex

## What does the ANS do?

*subconscious*,

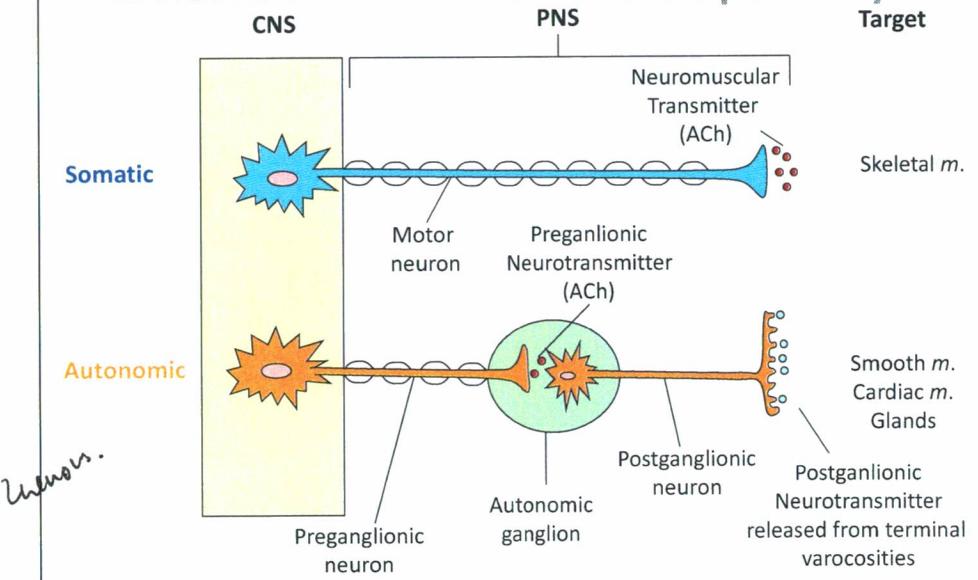
- The Autonomic Nervous System (ANS) innervates smooth *m.*, cardiac *m.*, and glands
- Controls critical body functions such as:
  - blood pressure
  - heart rate
  - temperature
  - digestion
  - elimination of wastes
- Mostly does this without our awareness or attention

# Differences



## Differences:

### 2 Neuron chains in autonomic pathways



### Terminal varicosities in postganglionic autonomic neurons

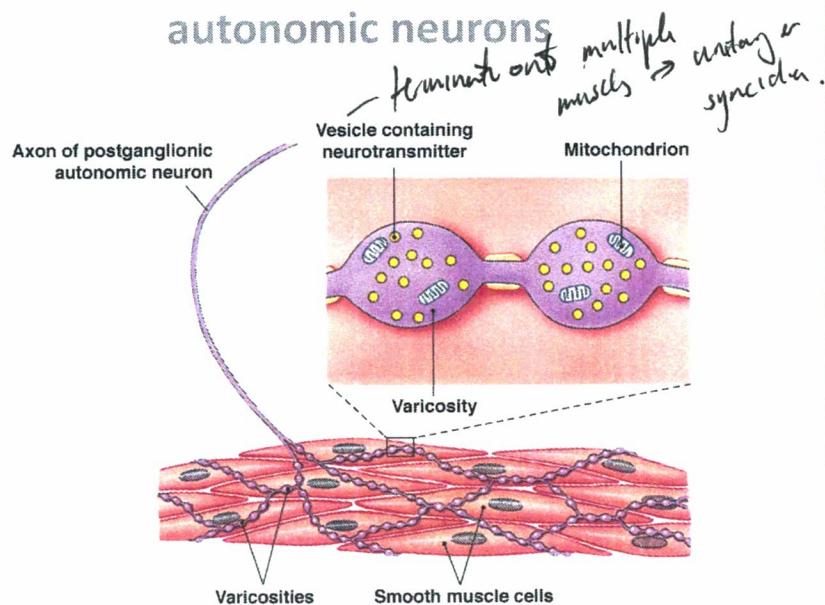


Figure 11-8

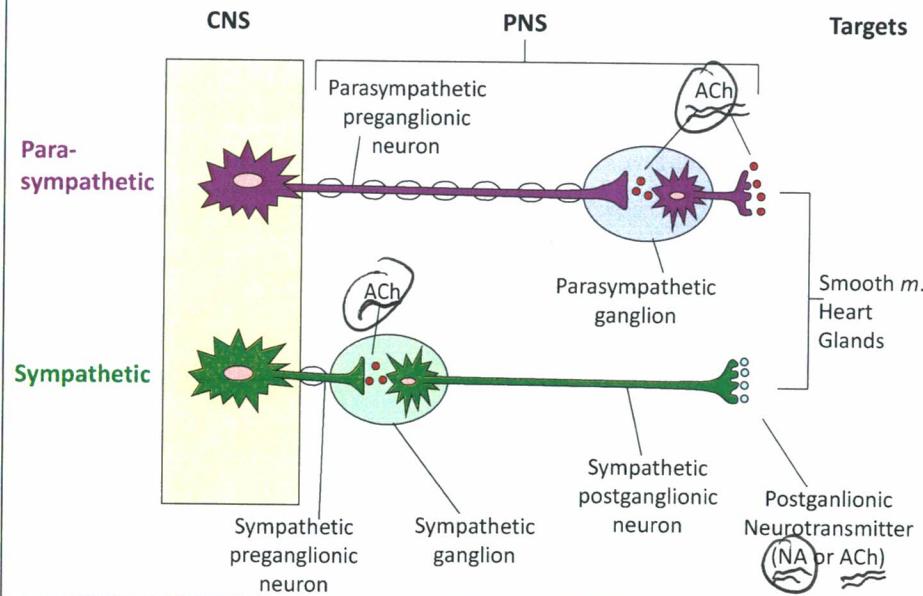
## Overview of Functions Parasympathetic vs. Sympathetic

- **Maintenance functions:**  
stores and conserves energy
  - Decreases HR
  - Promotes digestion
  - Constricts bronchioles
  - Promotes defecation & urination
  - Constricts pupils
  - Promotes energy storage

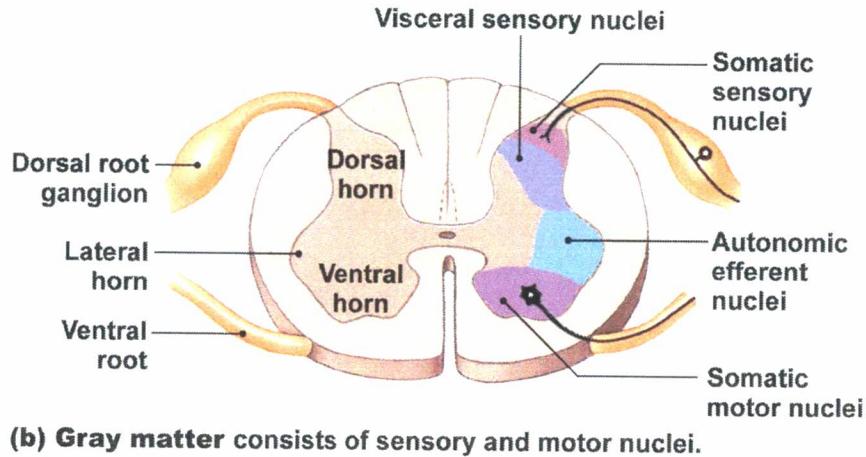
*diff function in diff part of body.*
- “Rest and Digest”

- **Stress response:**  
Prepares body to deal with emergencies
  - Increases HR
  - Inhibits digestion
  - Dilates bronchioles
  - Inhibits urine production and defecation
  - Dilates pupils
  - Mobilises energy stores
  - Constricts most BVs
  - Dilates BVs in SkM.
  - Stimulates sweat production
- “Fight or flight”

## Parasympathetic vs. Sympathetic



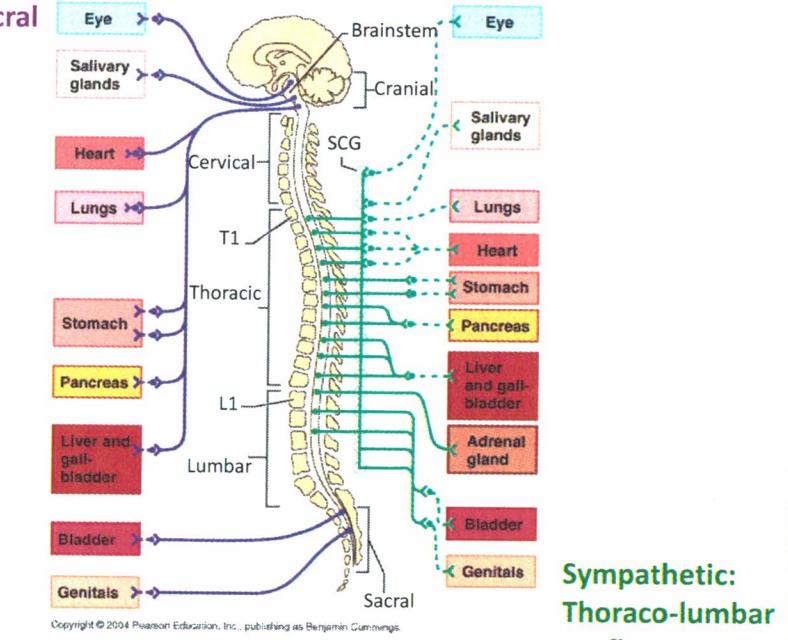
## The Lateral Horn



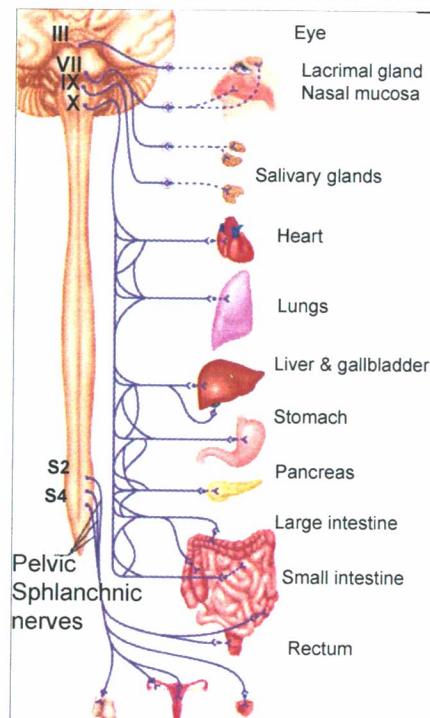
Silverthorn (5<sup>th</sup> Ed) Fig 9-7

### Parasympathetic:

#### Cranio-sacral outflow



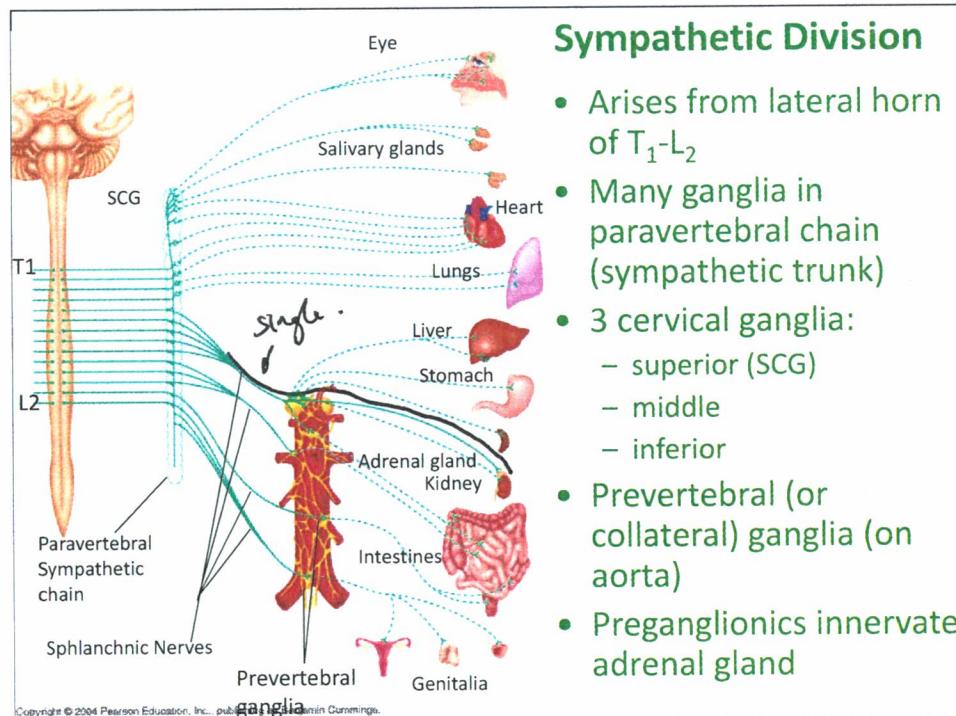
### Sympathetic: Thoraco-lumbar outflow



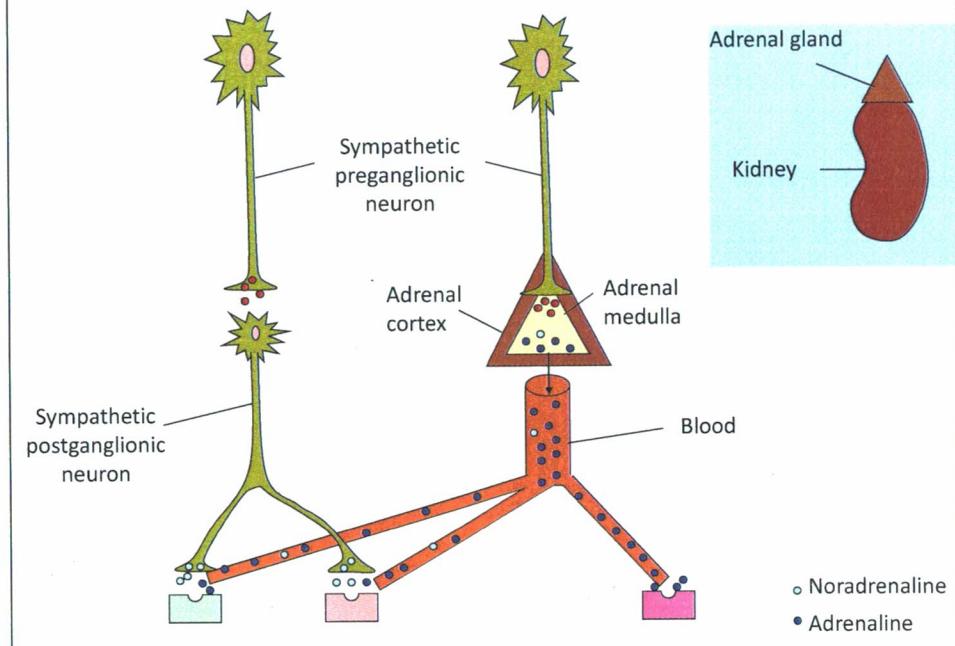
## Parasympathetic Division

- Cranial components arise from brainstem nuclei and fibres run with those of cranial nerves:
  - III: Oculomotor
  - VII: Facial
  - IX: Glossopharyngeal
  - X: Vagus
- Sacral fibres arise from the lateral horn of sacral cord segments S<sub>2</sub>-S<sub>4</sub>
- Synapse in ganglia close to target organs

] facial



## The Adrenal Medulla: part of the sympathetic nervous system



Characteristic	Parasympathetic	Sympathetic
Origin	Cranial and Sacral	Thoracic and Lumbar
Location of ganglia	Close to target	Distant from target
Relative length of fibres	Long preganglionic; Short postganglionic	Short preganglionic; Long postganglionic
Branching of preganglionics	Minimal	Extensive
Primary role	Maintenance	Emergencies; exercise
Neurotransmitters	All pre & post use ACh	All pre use ACh Most post use NA Some post use ACh (sweat glands & BVs of SkM) Adrenal gland releases circulating Adr. and NA

## Effect of ANS activity on different organs

Organ:	Parasympathetic Stimulation:	Sympathetic Stimulation:
Heart	Dec. rate & force of contraction	Inc. rate & force of contraction
Blood vessels	Dilation in genitals only	Constriction (mostly) Dilation in SkM
Lungs	Constriction of bronchioles	Dilation of bronchioles
Digestive Tract	Inc. motility & secretions	Dec. motility & secretions
Bladder	Contraction	Relaxation
Eye	Constriction of pupil Accommodation of lens	Dilation of pupil Relaxation of lens
Exocrine pancreas	Stimulation of secretion	Inhibition of secretion
Salivary glands	Stimulation (watery saliva)	Stimulation (mucous rich)
Endocrine pancreas	Stimulates insulin release	Simulates glucagon release

## Receptors & their Major Locations

### • Cholinergic: ACh

- Nicotinic: always excitatory
  - All ganglionic neurons
- Muscarinic: excitatory or inhibitory
  - All parasympathetic target organs
  - A few sympathetic target organs (sweat glands)

*preganglionic*

### • Adrenergic: Adr. & NA

- $\alpha_1$ : Most sympathetic targets including BVs to skin and viscera.  
NA > Adr. Excitatory. - *constriction*.
- $\alpha_2$ : Gastrointestinal tract. Inhibitory. NA>Adr.  
*relaxation*
- $\beta_1$ : Heart: equal affinity for NA and Adr. Excitatory.
- $\beta_2$ : Lungs, BVs in heart and skeletal muscle & other sympathetic target organs except heart. Adr>NA. Inhibitory. - *dilation*
- $\beta_3$ : Adipose tissue. Excitatory. NA>Adr.

*depending on receptor expression,  
we may have different effect*

## Dual Innervation & Dominance

- Most visceral structures receive sympathetic **and** parasympathetic innervation
  - Some exceptions: BVs, sweat glands
- Allows for more precise control over activity
- Both systems are usually partially active:
  - sympathetic tone
  - parasympathetic tone
- Shifts in the balance can be made to meet the needs of a specific organ/system or as a generalised response
  - E.g., relaxing after meal vs. emergency



## Clinically important agonists & antagonists

- Due to differential distribution of receptors throughout body, drugs can selectively enhance or block responses in different organs

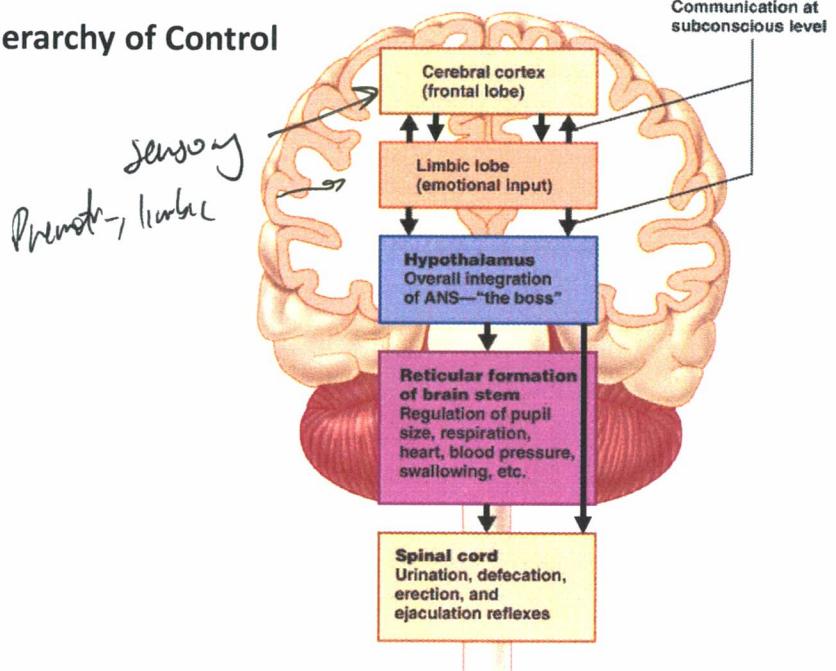
### - Salbutamol activates $\beta_2$ adrenergic receptors:

- used to dilate bronchioles without affecting heart in asthma patients

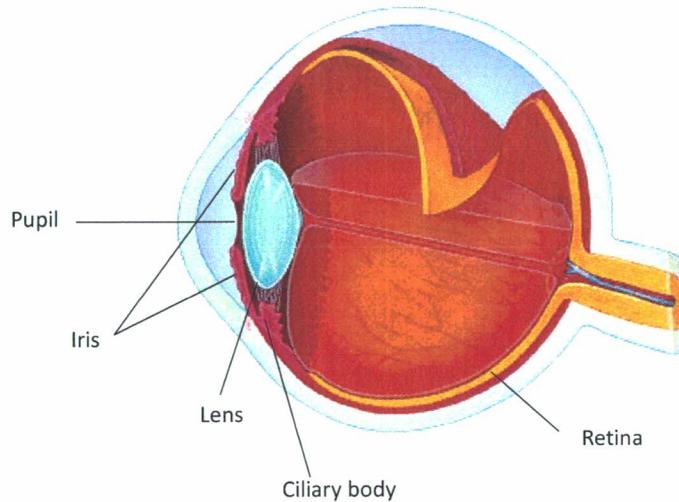
### - Atropine acts on muscarinic receptors:

- blocks parasympathetic without affecting sympathetic. Used to decrease salivary and bronchial secretions during surgery

## Hierarchy of Control

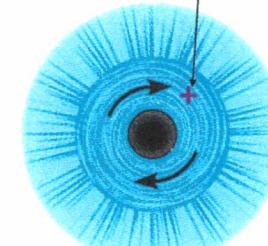


## Structure of the eye



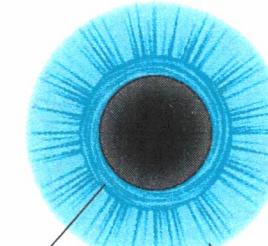
## Autonomic innervation of the iris

Parasymp. stimulation:  
circular m. contracts



Pupillary constrictor m.

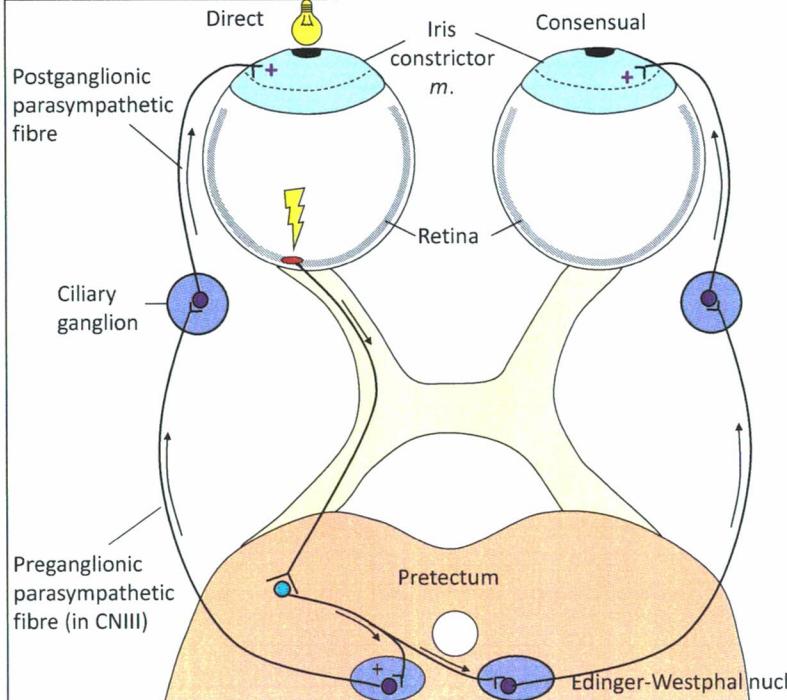
Symp. stimulation:  
radial m. contracts



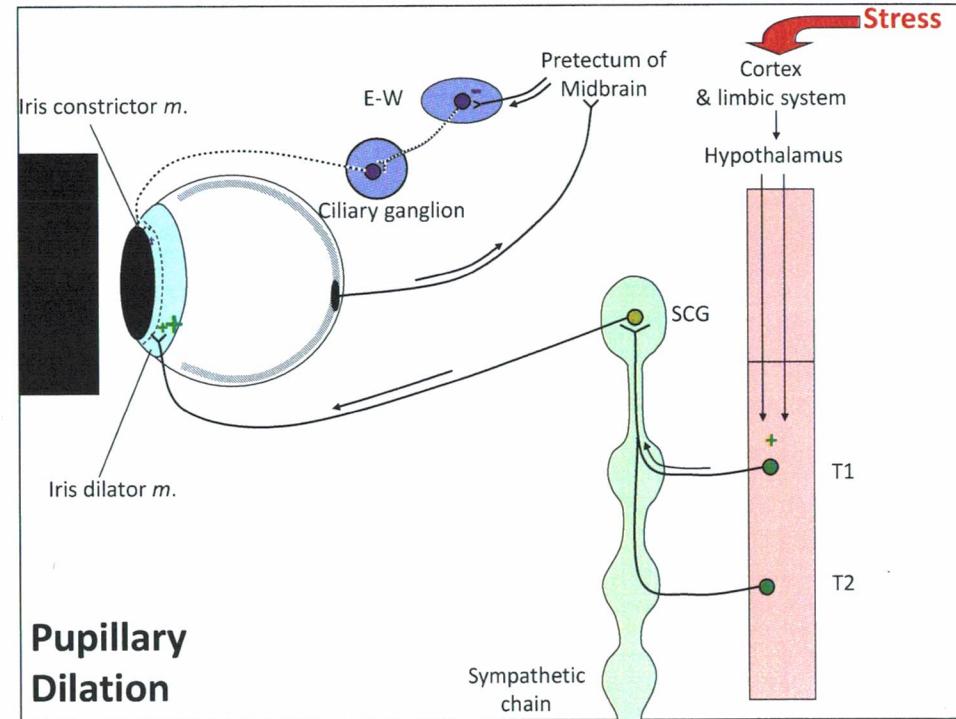
Pupillary dilator m.

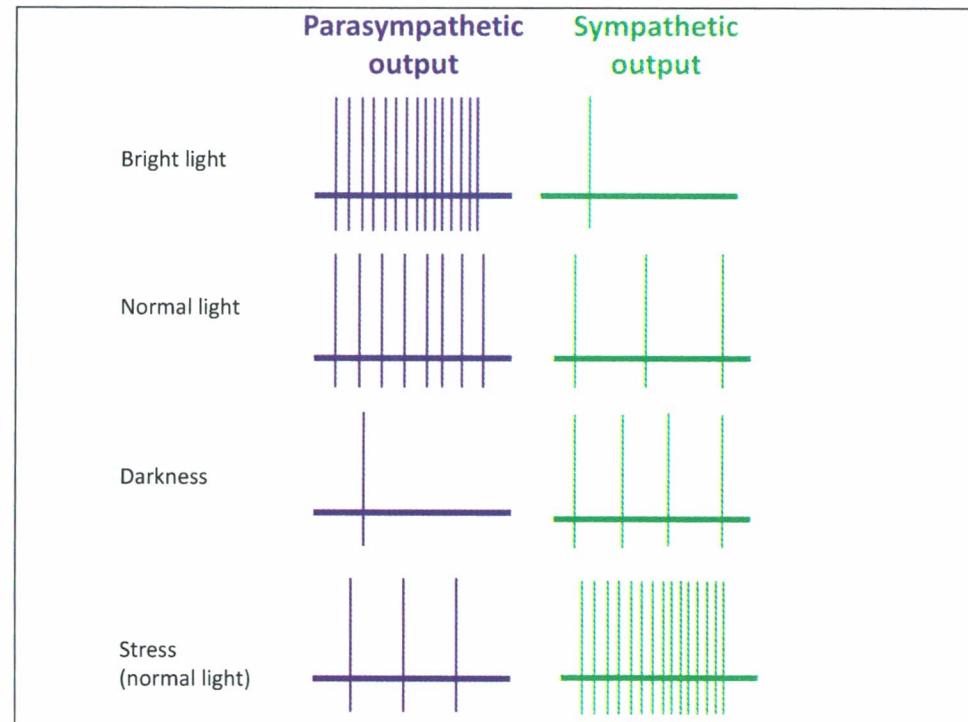
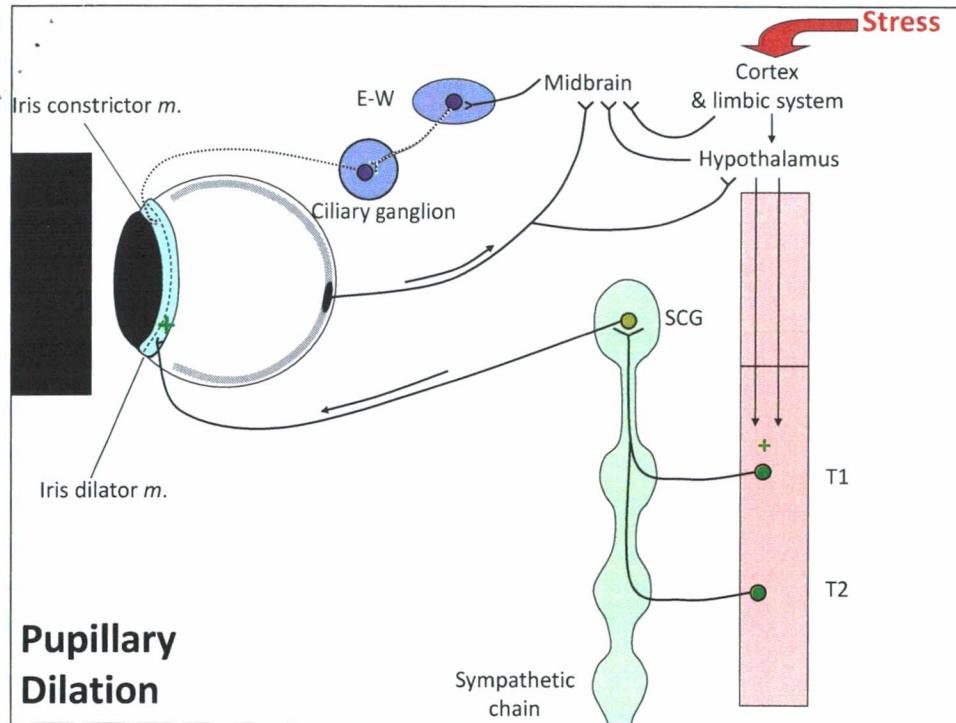
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## Pupillary Light Reflex



## Pupillary Dilation





## Learning Objectives

- Describe the structure and functions of the ANS noting similarities and differences with the somatic nervous system
- Describe structural and functional features of sympathetic and parasympathetic divisions of ANS
- Describe the physiological significance of cholinergic and adrenergic receptors and their major subtypes (Explain how they relate to the clinical importance of atropine and salbutamol)
- Outline the function of the adrenal gland
- Explain the physiological significance of dual innervation, and relate this to sympathetic vs. parasympathetic dominance on major organ systems during flight-or-fight vs. resting states
- Describe the hierarchical central control of the ANS
- Explain the pupillary reflexes in terms of the autonomic innervation of the circular and radial muscles of the iris

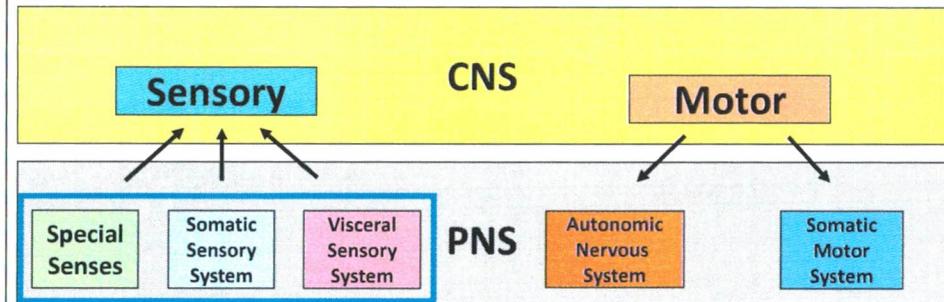
# Sensation

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## What is it?



Sensory component

# Stimulus Processing

### Information Processing by the Sensory Division

Table  
10.1

#### Stimulus Processing Usually Conscious

Special Senses	Somatic Senses	→ throughout the body
Vision	Touch	
Hearing	Temperature	
Taste	Pain	
Smell	Itch	
Equilibrium	Proprioception	

*sensors are in the head*

*(modality - specific & changes in type of area)*

*] perception*

### Information Processing by the Sensory Division

Table  
10.1

#### Stimulus Processing Usually Subconscious

Somatic Stimuli	Visceral Stimuli
Muscle length and tension	Blood pressure
Proprioception	Distension of gastrointestinal tract
	Blood glucose concentration
	Internal body temperature
	Osmolarity of body fluids
	Lung inflation
	pH of cerebrospinal fluid
	pH and oxygen content of blood

*monitored subconsciously  
→ feed to CNS  
& activate what occurs appreciation*

# Types of Receptors

Types of Sensory Receptors

Table  
10.2

Type of Receptor	Examples of Stimuli
Chemoreceptors	Oxygen, pH, various organic molecules such as glucose
Mechanoreceptors	Pressure (baroreceptors), cell stretch (osmoreceptors), vibration, acceleration, sound
Photoreceptors	Photons of light
Thermoreceptors	Varying degrees of heat

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sensit & certain stimuli .

modality depends on change of energy

## Sensory Transduction

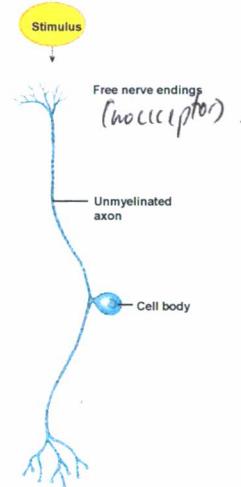
→ convert to chemical & electrical signals .

- Stimulus energy converted into information processed by CNS
  - Ion channels or second messengers initiate membrane potential change (receptor potential)
- Threshold: Minimum stimulus to drive activation

nearby threshold, lead to AP to CNS .

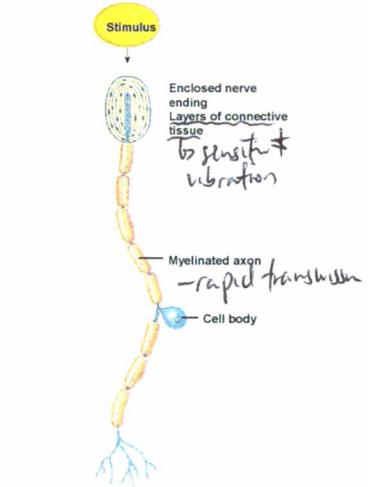
# Types of Receptors

(a) Simple receptors are neurons with free nerve endings. They may have myelinated or unmyelinated axons.



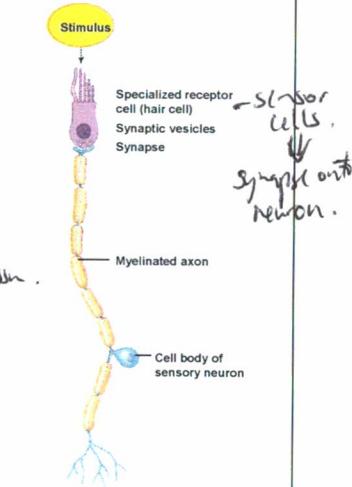
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(b) Complex neural receptors have nerve endings enclosed in connective tissue capsules. This illustration shows a Pacinian corpuscle, which senses touch.



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(e) Most special senses receptors are cells that release neurotransmitter onto sensory neurons, initiating an action potential. The cell illustrated is a hair cell, found in the ear.



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sensor cells .  
synapse onto neuron .

## Sensory Pathways

AP → integrate with CNS .

Transduce energy to an electro-chemical signal (e.g. change in  $V_m$ )

Detect (physical energy) changes in conditions

Stimulus reaches threshold: APs along afferent pathway

Plan, prepare and execute motor commands

Effectors

## Integration by CNS

- Sensory information
    - Indirectly to brain by ascending pathways
    - Directly to brain stem via cranial nerves
  - Visceral reflexes integrated in brain stem or spinal cord usually do not reach conscious perception
  - Perceptual threshold: level of stimulus necessary to be aware of particular sensation

Sensor needs to activate by exceeding receptor potential threshold.

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# Modality

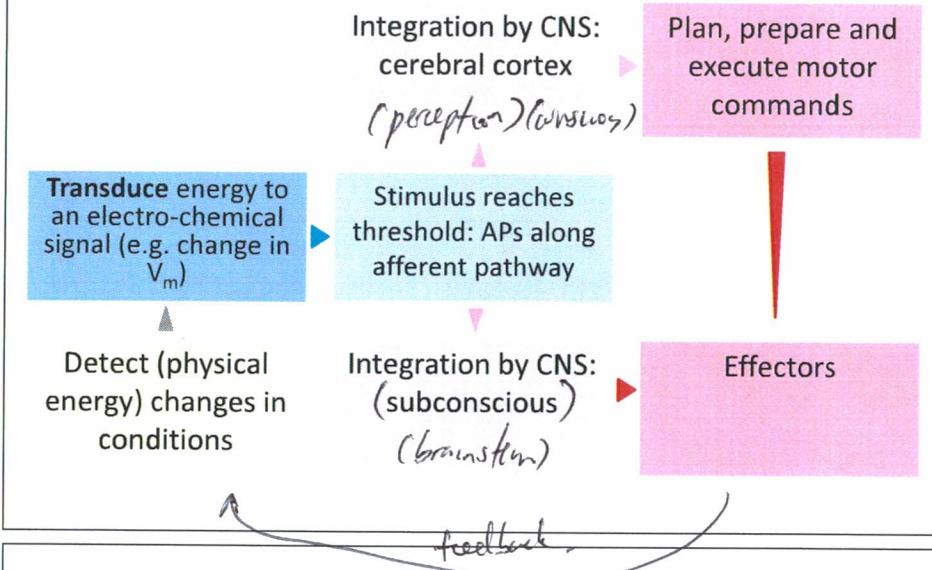
- Indicated by
    - Location of sensory activation
    - Area of primary processing within brain
  - Specificity
    - Each receptor type is most sensitive to a particular modality of stimulus
  - Labeled line coding
    - Modal specific circuitry

Each receptor type is most sensitive to a particular modality of stimulus labeled line coding

Sensors only respond to specific modalities.

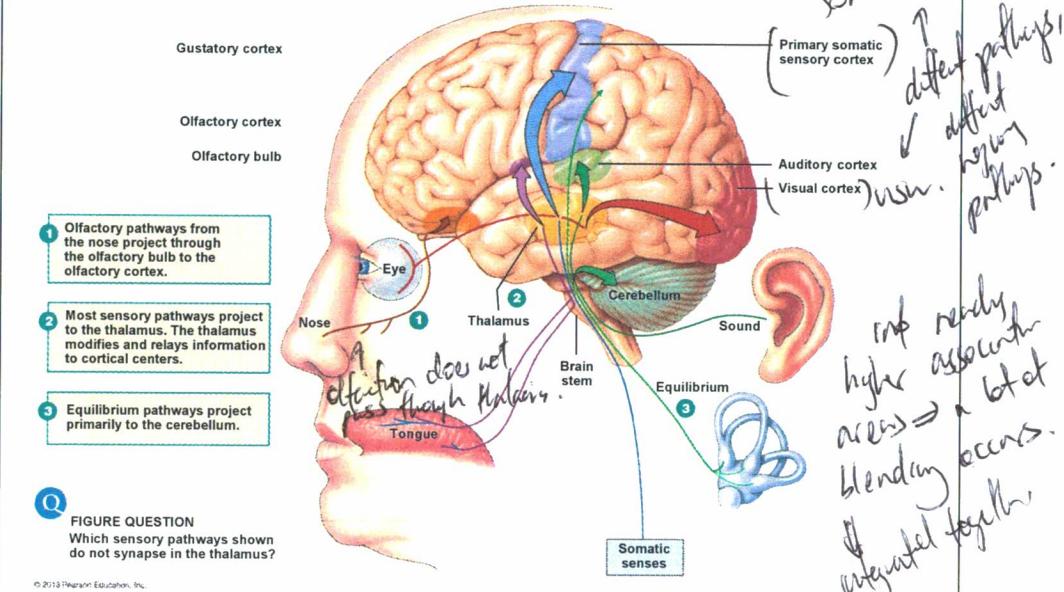
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## Sensory Pathways



SENSORY PATHWAYS IN THE BRAIN

Most pathways pass through the thalamus on their way to the cerebral cortex.



## Location

- Depends on which **receptive fields** are activated (can vary depending on modality)
- Receptive field:** Region of space that will drive activation of sensory neurons

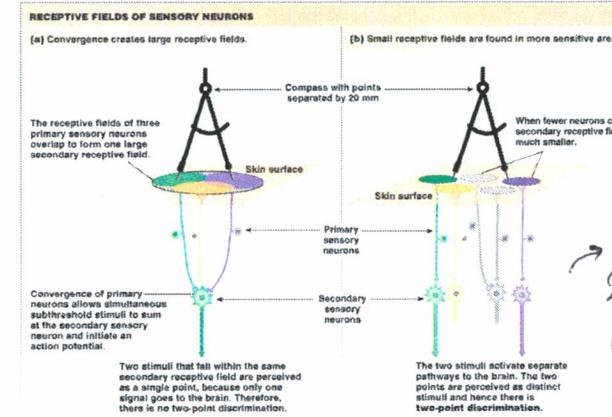
disambiguate different types of stimuli

## Sensitivity

- Lateral inhibition
  - Increases contrast between activated receptive fields and inactive neighbors

non-complex stimulus  
→ increase contrast

## Receptive fields



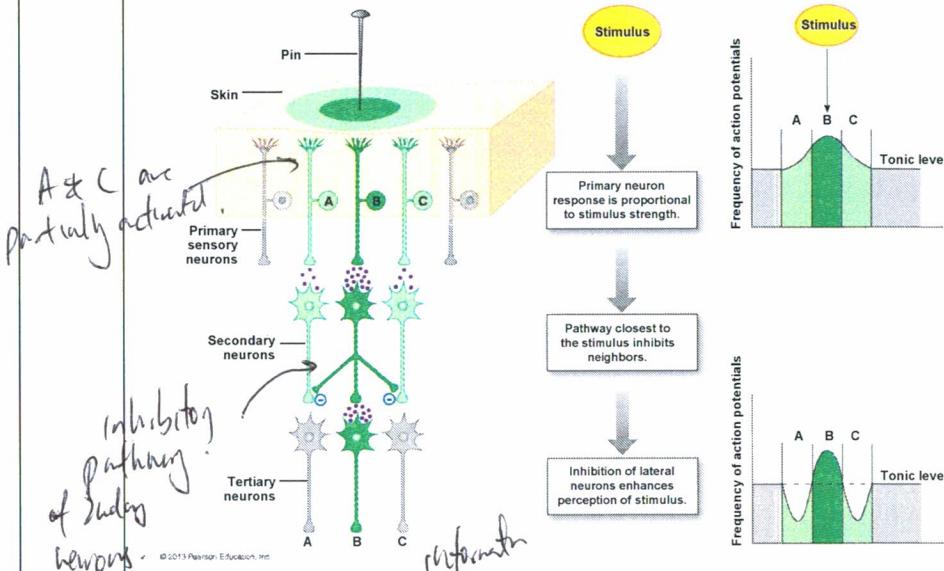
same secondary synapse

→ secondary neuron integrates all 3 receptors.

→ large receptive field for 2nd order neuron.  
→ can't distinguish each individual receptive field.

1st synapse, departs  
2nd order neuron,  
info continued on as  
separate at level of  
2nd order neuron.  
↪ ability of neurons  
differ, increases  
greater acuity

### LATERAL INHIBITION



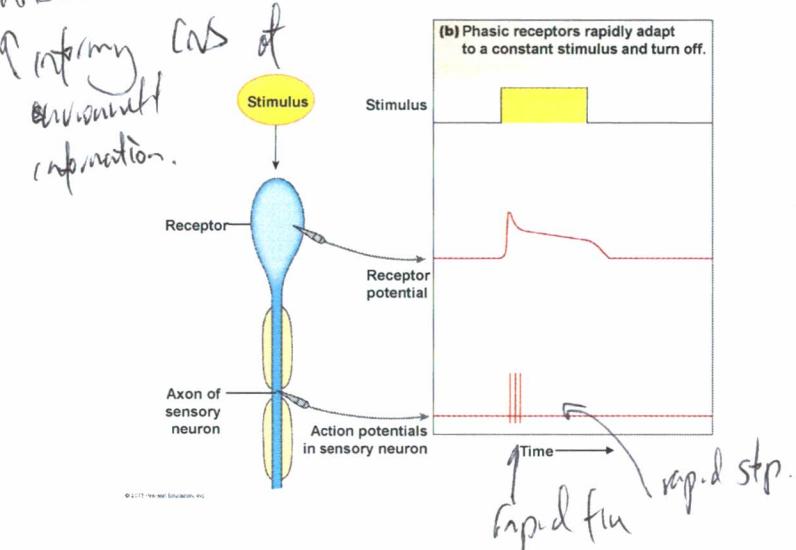
# Sensitivity and Duration

- Sensitivity
  - Coded by number of receptors activated and frequency of action potentials
- Duration
  - Coded by duration of action potentials
  - Some receptors can **adapt**, or cease to respond
- Tonic receptors versus phasic receptors

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## Adaptation

PHASIC

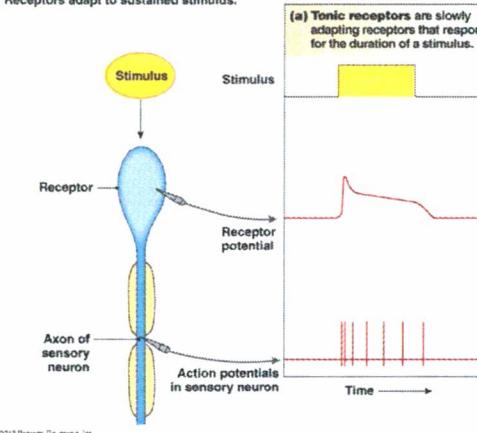


## Adaptation

Tonic .

### RECEPTOR ADAPTATION

Receptors adapt to sustained stimulus.



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## Summary and Objectives

- Sensory systems and relevant concepts

# Somatic Senses

## Modality

Ia, II

- Proprioception - golgi tendon organ & muscle spindles.
- Temperature
- Nociception
- Touch

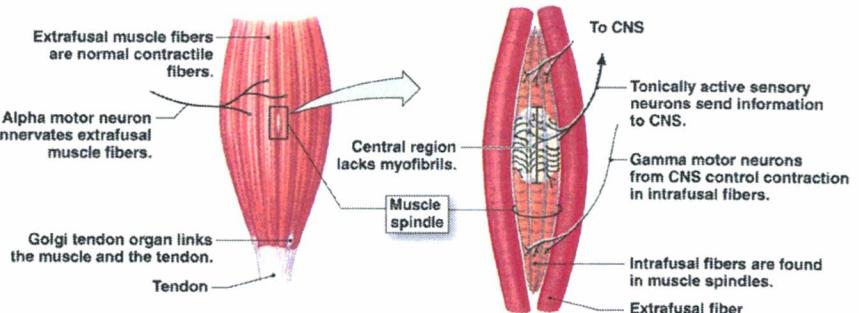
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## Types of Receptors

RECEPTOR	STIMULUS	LOCATION	STRUCTURE	ADAPTATION
Free nerve endings	Temperature, noxious stimuli, hair movement	Around the hair roots and under surface of skin	Unmyelinated nerve endings	Variable
Meissner's corpuscles	Flutter, stroking	Superficial layers of skin	Encapsulated in connective tissue	Rapid
Pacinian corpuscles	Vibration	Deep layers of skin	Encapsulated in connective tissue	Rapid
Ruffini corpuscles	Stretch of skin	Deep layers of skin	Enlarged nerve endings	Slow
Merkel receptors	Steady pressure, texture	Superficial layers of skin	Enlarged nerve endings	Slow

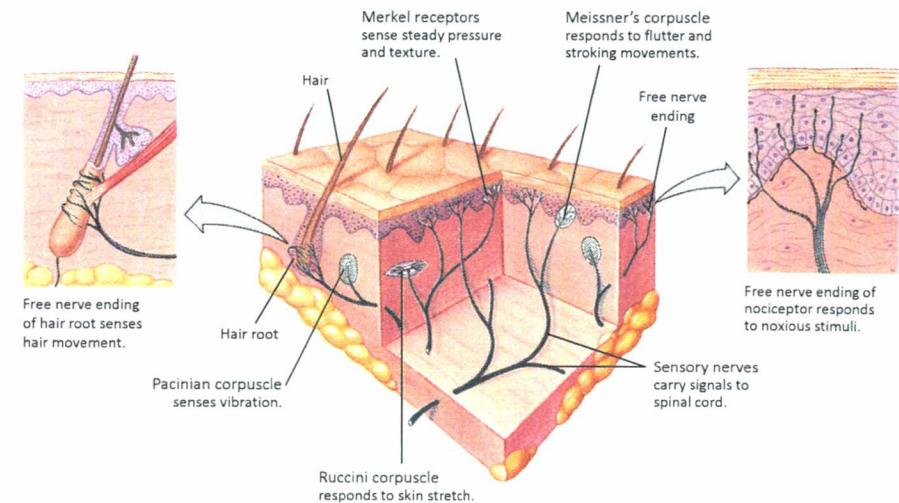
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# Proprioception



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## Types of Receptors



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## Temperature

- Free nerve endings (relatively slow)
- Terminate in subcutaneous layers
- Detects temperature changes
- Cold receptors
  - Lower than body temperature
- Warm receptors
  - Above body temperature to about 45 °C
  - Pain receptors activated above 45 °C
  - Adapts depending on temperature
  - Adapts between 20 ~ 40 °C

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no persistent (adaptation) normally  
→ ~~pain~~, receptors will not adapt and will activate nociceptors (damaging stimuli)

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## Nociceptors

- Respond to strong noxious stimulus that may damage tissue
- Free nerve endings
- Non-adapting

## Nociceptor Pathways

- Reflexive protective response
  - Integrated in spinal cord
  - Withdrawal reflex ↙ away from noxious stimuli
- Ascending pathway to cerebral cortex
  - Becomes conscious sensation (pain or itch)

Classes of Somatosensory Nerve Fibers

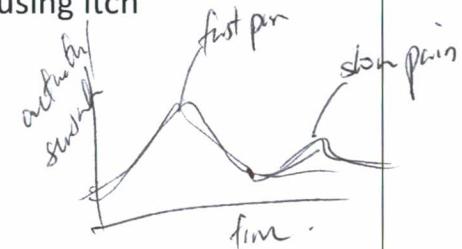
Table 10.3

Fiber Type	Fiber Characteristics	Speed of Conduction	Associated With
A $\beta$ (beta)	Large, myelinated	30–70 m/sec	Mechanical stimuli
A $\delta$ (delta)	Small, myelinated	12–30 m/sec	Cold, fast pain, mechanical stimuli
C	Small, unmyelinated	0.5–2 m/sec	Slow pain, heat, cold, mechanical stimuli

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## Nociceptors: Pain and Itch

- Itch *inflammatory response, activating C fibers directly*
  - Histamine activates C fibers, causing itch
  - From skin nociceptors
- Pain
  - Subjective perception
  - Fast pain
    - Sharp and localized—by A $\beta$  fibers
  - Slow pain
    - Duller and more diffuse—by C fibers



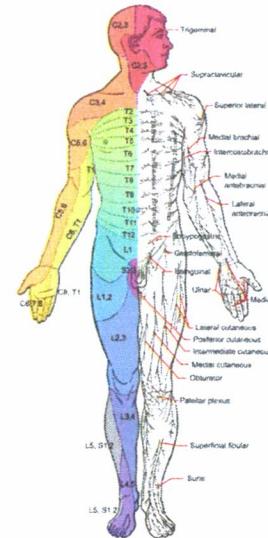
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# Touch

## Location

- Location specific *highly location.*
- Dermatome
- Perception topographically mapped
- Sensory homunculus

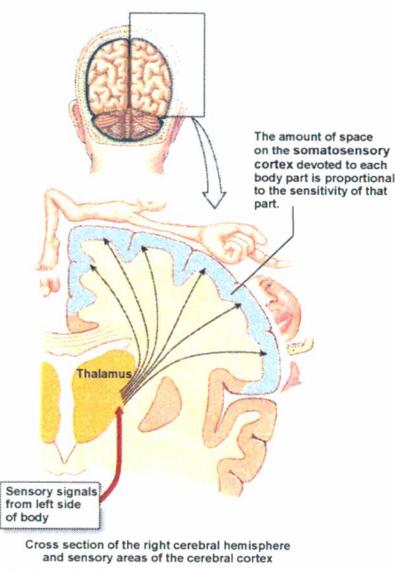
# Dermatome



[https://upload.wikimedia.org/wikipedia/commons/d/db/Dermatomes\\_and\\_cutaneous\\_nerves\\_-anterior.png](https://upload.wikimedia.org/wikipedia/commons/d/db/Dermatomes_and_cutaneous_nerves_-anterior.png)

### THE SOMATOSENSORY CORTEX

Each body part is represented next to the area of the sensory cortex that processes stimuli for that body part. This mapping was created by two neurosurgeons, W. Penfield and T. Rasmussen, in 1950 and is called a homunculus (little man).



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# Sensation

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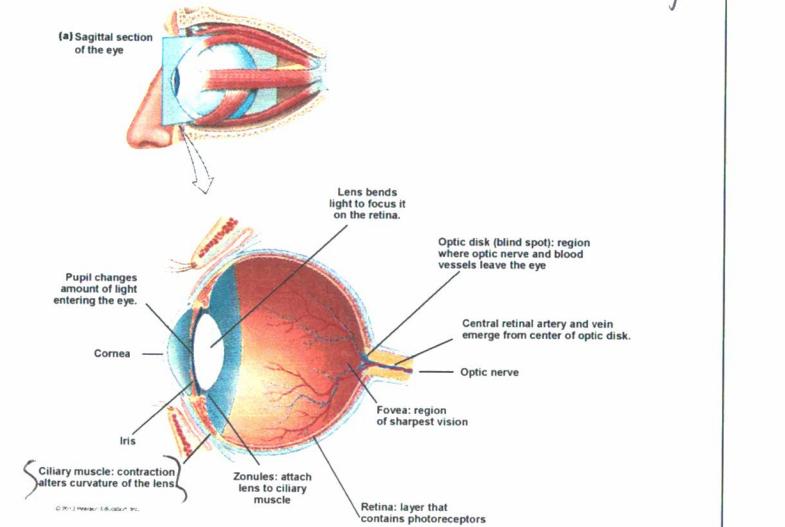
Vision - speed sun.  
photoreceptors.  
eyes → signals. wmp

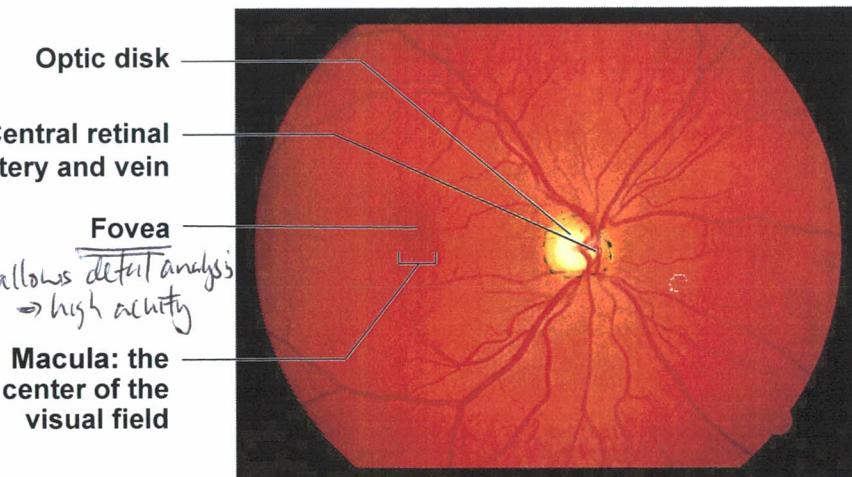
- Energy: Light (Photons)
- Photo-transduction: photoreceptors within retina
- Sensory information processed at multiple stages along neural pathway
- Visual perception

# Vision

- Introduction
- Eye
- Retina
- Visual pathways and targets
- Visual cortex

## Eye





(b) View of the rear wall of the eye as seen through the pupil with an ophthalmoscope

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## Eye

- Lens
  - Focuses light
    - Refraction
    - Accommodation
      - Lens shape adjusts to keep objects in focus

## Eye

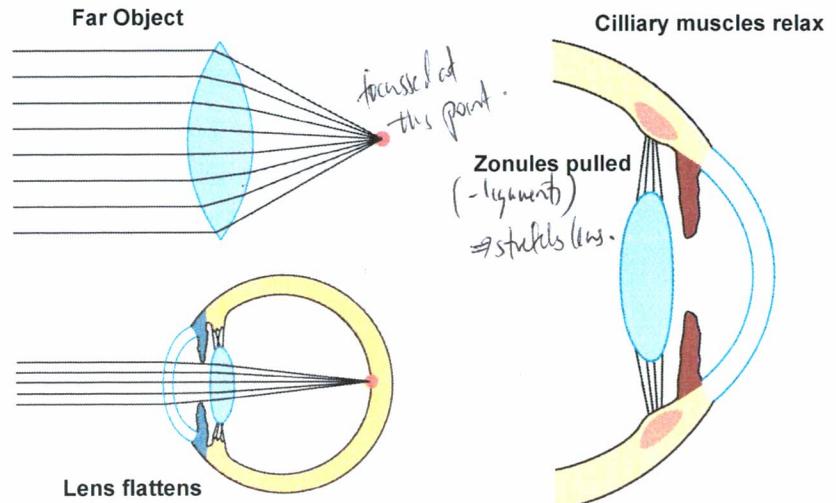
DOF = depth of focus.

- Pupil

- Aperture of the eye
  - Modulates light reaching retina
  - Depth of focus
    - Range behind lens where image remains acceptably sharp
    - Constriction of pupil (smaller aperture) leads to an increase in DOF (smaller circle of confusion)

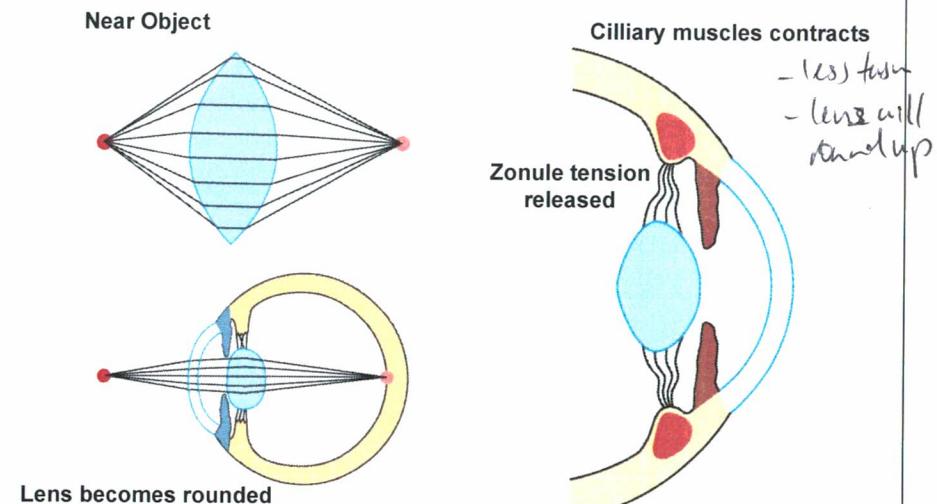
aperture low = light input with parallel

## Accommodation



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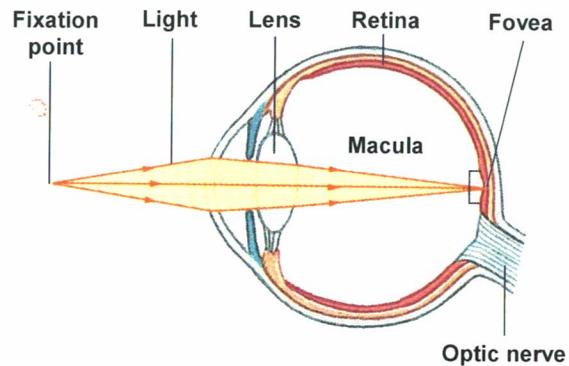
## Accommodation



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## Retina

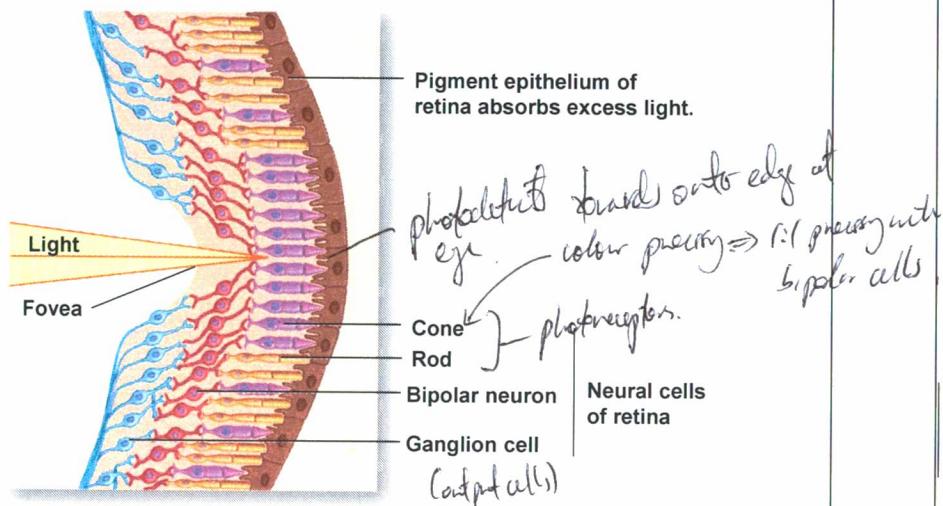
(a) Dorsal view of a section of the right eye



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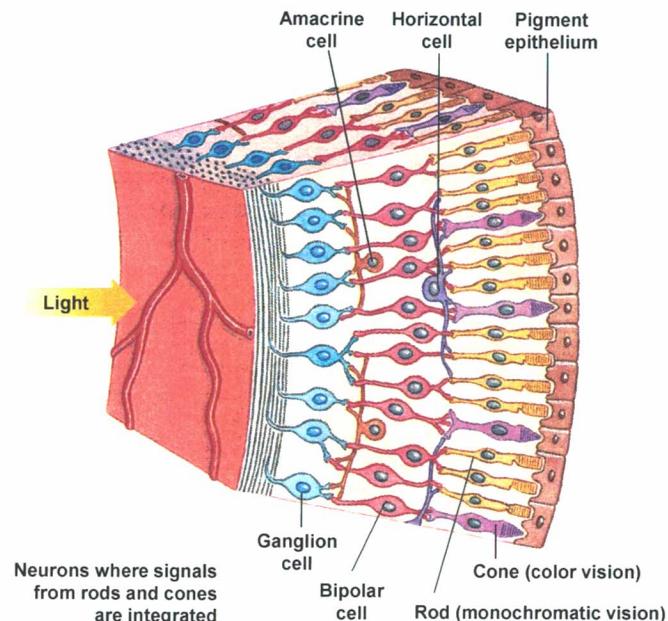
## Retina

(d) Light strikes the photoreceptors in the fovea directly because overlying neurons are pushed aside.



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(f) Retinal photoreceptors are organized into layers.



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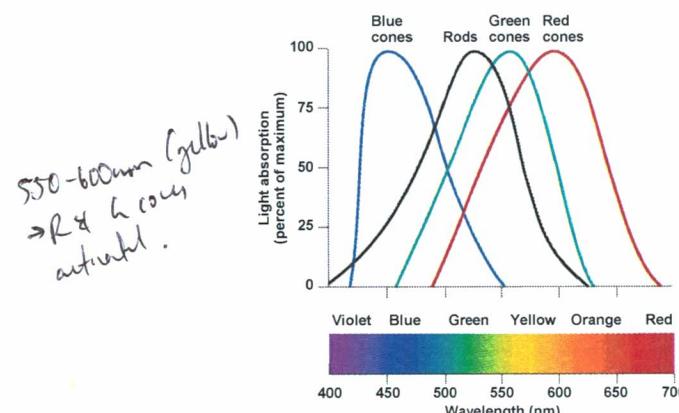
# Photoreceptors

- Rods function well in low light and are used in night vision  
- (b/w)
- Cones are responsible for high-acuity vision and vision during the daytime - color.
- Visual pigments convert light energy into a change in membrane potential
  - Rods contain rhodopsin
  - Cones contain three pigments

# Photoreceptors

## LIGHT ABSORPTION BY VISUAL PIGMENTS

There are three types of cone pigment, each with a characteristic light absorption spectrum. Rods are for black and white vision in low light.



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# Phototransduction

- Rods (in the dark)
  - CNG and K<sup>+</sup> channels open (tonic release of glutamate)
  - Light activates rhodopsin *(from retinal & opsin)* (phosphodiesterase)
  - Activates transducin which in turn activates PDE
  - PDE hydrolyzes cGMP
  - Decreased levels of cGMP close CNG channels
  - Cell hyperpolarizes decreasing glutamate release
  - On bipolar cells activated with decreased glutamate (mGluR6)

Rods tonically depolarized.  
cGMP keeps CNG channels open.

light reduces release.

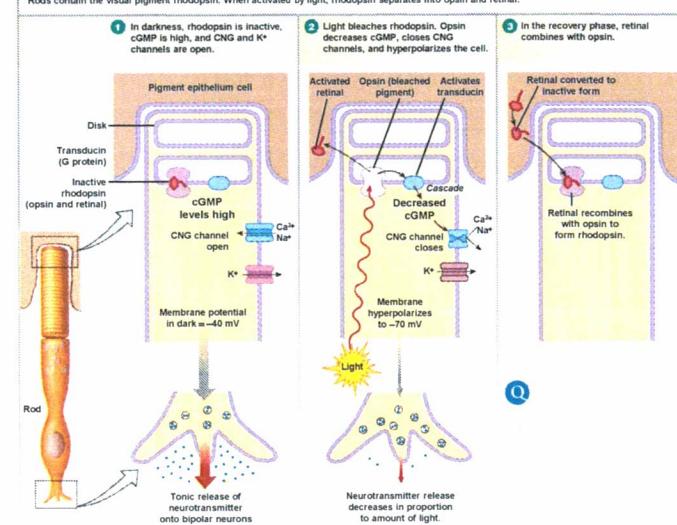
glutamate

light reduces release.

glutamate

## PHOTOTRANSDUCTION IN RODS

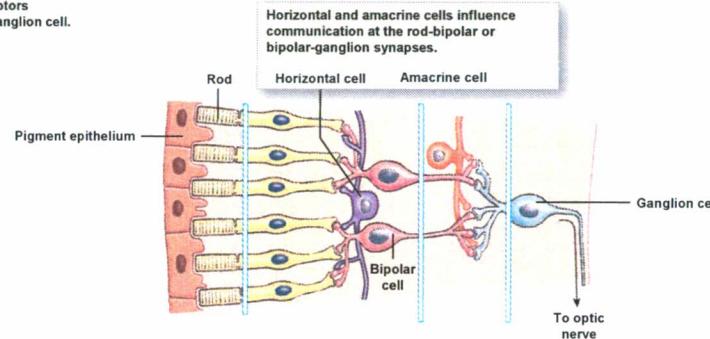
Rods contain the visual pigment rhodopsin. When activated by light, rhodopsin separates into opsin and retinal.



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# Retina

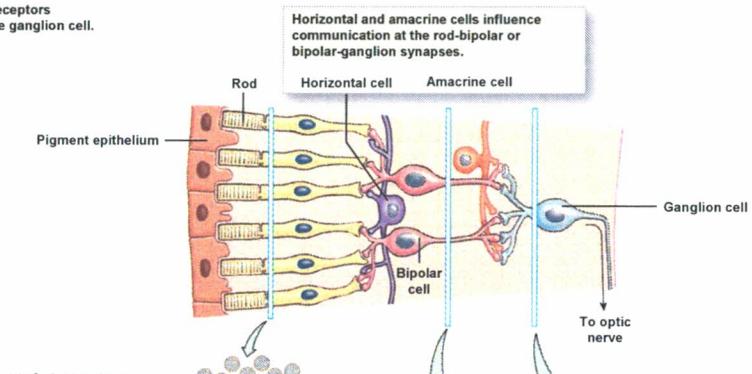
(a) Multiple photoreceptors converge on one ganglion cell.



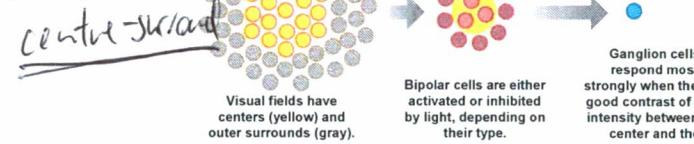
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Figure 10.33a-b (1 of 4)

(a) Multiple photoreceptors converge on one ganglion cell.



(b) A group of adjacent photoreceptors form the visual field for one ganglion cell. This illustration shows an on-center, off-surround field.



Ganglion cells respond most strongly when there is good contrast of light intensity between the center and the surround.

# Receptive Fields

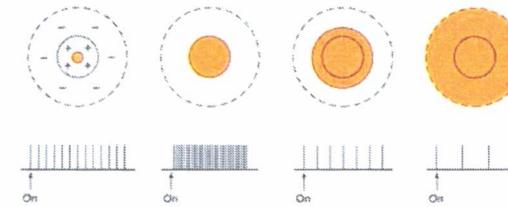
(c) The retina uses contrast rather than absolute light intensity for better detection of weak stimuli.

Visual field type	Field is on-center/off-surround	Field is off-center/on-surround
On-center, off-surround	Bright light onto center 	Ganglion cell is excited by light in the center of the visual field. Ganglion cell is inhibited by light in the center of the visual field.
Off-center, on-surround	Bright light onto surround 	Ganglion cell is inhibited by light on the surround of the visual field. Ganglion cell is excited by light on the surround of the visual field.
Both field types	Diffuse light on both center and surround 	Ganglion cell responds weakly. Ganglion cell responds weakly.

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# Receptive Fields

center surround aspect allows for



Adapted from Hubel and Wiesel, 1961