Particles tend to move down their concentration gradients [Fick's 1st Law]

$$J = -D\frac{d\varphi}{dt}$$

However, the diffusion of particles is influenced by the presence of other particles in the mixture. So, we use the Chemical potential to take into account all the mass and charge related energetics when quantifying diffusion.

$$j_i = -\frac{D_i}{RT} c_i \frac{\partial \mu_i}{\partial x}$$

$$\mu_i = \mu_0 + RT\ln(\gamma_i C_i) + z_i F \phi_i$$

($\gamma_i C_i = a_i$)

- Mass related energetics
- Charge related energetics.

$$\mu_i = \left(\frac{\partial U}{\partial N_i}\right)_{S,V,N_{j\neq i}}$$

- Thermodynamic Potential Completely describe System
- Internal energy State function
- Nº of Particles
- Total effect of one particle on the system

Ions tend to move down their electrochemical gradient until equilibration is reached.

This can be across a membrane.

At thermodynamic equilibrium

$$\mu_{out} = \mu_{in}$$

$$\Rightarrow \mu^{\circ}_{out,i} + RT\ln(\gamma_i C_{out}) + z_i F \phi_{out} = \mu^{\circ}_{in,i} + RT\ln(\gamma_i C_{in}) + z_i F \phi_{in}$$

$$\Rightarrow RT\ln\left(\frac{C_{out}}{C_{in}}\right) = zF(\phi_{in} - \phi_{out})$$

$(\phi_{in} - \phi_{out})$: This represents the membrane potential at Thermodynamic equilibrium.

It is the Nernst Potential E.

→ At this point, the electric gradient and Chemical gradient balance each other

$$J_{Na^+} = -D\frac{d\varphi_{Na^+}}{dx}$$

$$E_{Na^+} = \frac{RT}{zF}\ln\left(\frac{[Na^+]_{out}}{[Na^+]_{in}}\right)$$

* e.g. The electric field induced by Na^+ outside is balanced by the electric field of K^+ or something like that...

Divide elements & prevent each of them from collapsing to entropy → life...

Taking Contribution from all important ions, we get GHK → It estimates resting membrane potential

↳ NOT Equilibration Potential !!

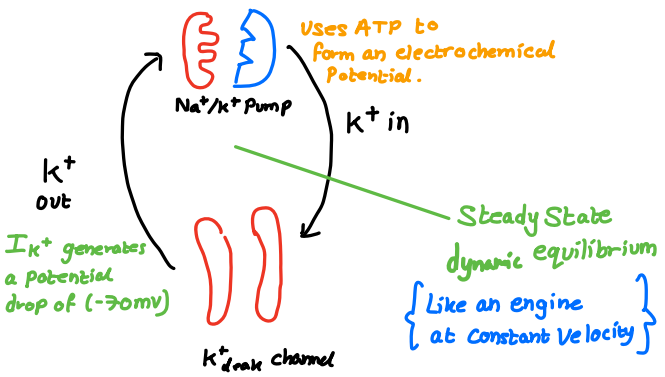
It reflects the reality of the membrane by:

1) accounting for multiple ions
2) Selective Permeability

} Ions are not at their individual equilibrium potential at Resting membrane potential → The whole membrane System is however at equilibrium → The cell has control over * the equilibrium point by being more selective to certain ions.

Note: In neurones, the selectivity for K^+ dominates that for Na^+ or Cl^-. K^+ has greater weight on the resting membrane potential and the RMP approximates the Nernst Potential for K^+.

↳ The efflux of K^+ through leak channels (as it wants to reach equilibrium) contributes to $V_m \approx E_{K^+}$



GHK:

Can also be derived by $\sum \mu_i$ each species

$$E_m = \frac{RT}{F} \ln \frac{P_K [K^+]_{out} + P_{Na} [Na^+]_{out} + P_{Cl} [Cl^-]_{in}}{P_K [K^+]_{in} + P_{Na} [Na^+]_{in} + P_{Cl} [Cl^-]_{out}}$$

Maintainance of RMP: Na^+/K^+ push $3Na^+$ out & $2K^+$ in

K^+ flow back out.

↳ Too much work if push only K^+ in. Easier to exchage $3Na^+$ for $2K^+$ and just be less selective to Na^+ so it does not come back in.

Brillant!!

Disturbing The Membrane Potential

↳ For a car running at constant velocity, hit gas pedal, intake manifold opens making pistons fire faster

↳ Causing an acceleration.

↳ Add internal energy, system moves to new eq. Point

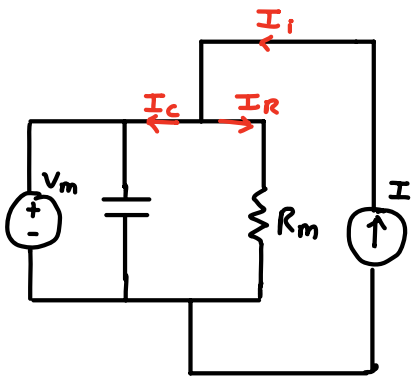
"quasi static Process" — Work" done

↳ Not exactly!!

How does a cell react?

↳ The V_m rises to a new Steady State upon Current injection.

↳ It decays back to V_m after halting ion flux.



① At equilibrium, Capacitor is at V_m and there is no current to and from the component

② Injection of I_i will cause the capacitor to charge to a new steady state potential

③ By KCL, $I_i = I_C + I_R$

- $C\frac{dV_m}{dt}$ (Storing Charge) → I_C Proportional to how fast V_m is Changing.
- $\frac{V_m}{R_m}$ (Ionic Flow) → I_R's Proportional to membrane potential
  - ↳ I_R changes too as V_m is Changing
    - As the membrane potential rises, so does the tension between outside and inside on the ions. They respond to the increase in V_m by surging in (forming a current) to form a new equilibrium.
    - I_R moves from I_{Rest} to I_{new}
    - ↳ Driving Force

④ Charging:

$$V_m(t) = V_0 + V_{max\ new}\left(1 - e^{-t/\tau}\right)$$

$\begin{cases} t=0, V_m = V_0 \\ t=\infty, V_m = V_{max} \end{cases}$

$\tau = RC$ ↓ If τ larger, membrane take more time to reach max value.

$$I_{ion} = g_{ion}(V_m - E_{ion})$$

I_{ion} ↓ Fixed

$I_{ion}(t)$ $V_m(t)$

As Capacitor charges V_m rises ⇒ I_{ion} increases

When Capacitor finish chaging despite Current Source still providing current

$I_i = \cancel{I_C}^{\,0} + I_R \Rightarrow I_C \approx I_R$

New equilibrium $I_{ion\ new} = g_{ion}(V_{max} - E_0)$

Old equilibrium $I_{ion\ rest} = g_{ion}(V_{rest} - E_0)$

I_{ion} still flowing through pore but it cause no change to V_m

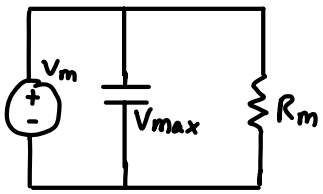
Steady State

⑤ Switching off the Current Source

Decay back to initial resting equilibrium.

$$V_m(t) = V_{max} e^{-t/\tau} (+V_{rest})$$

$e^{-t/\tau} \to 0$ as $t \to \infty$



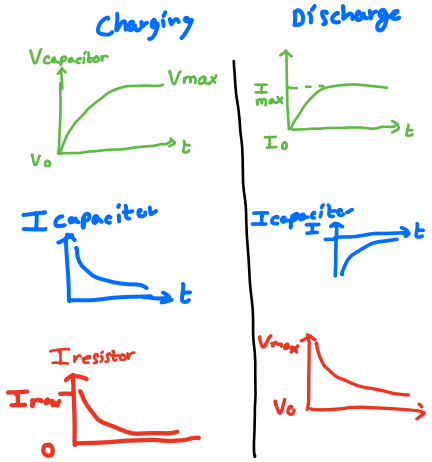
$$C_m \frac{dV_m}{dt} = -\frac{V_m}{R_m}$$

Discharge of capacitor

Provides opposing current to resistor → deceleration of equilibrating ion flux.

Since Vm decreases to lower initial value, the new equilibrium point has a lower rate of (equilibrium maintaining) ion flux → $V_m = V_{rest}$, $I_{ion} = I_{ion\ rest}$

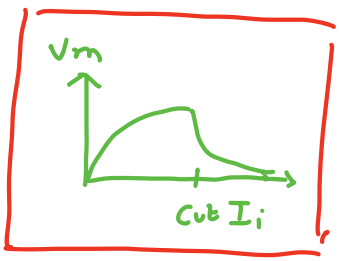
Plots



If no capacitor, I_R increases linearly as I_i is injected

$$I_{new} = \frac{V_m}{R} + I_i$$

↳ from resting equilibrium mechanism



Graded Potential

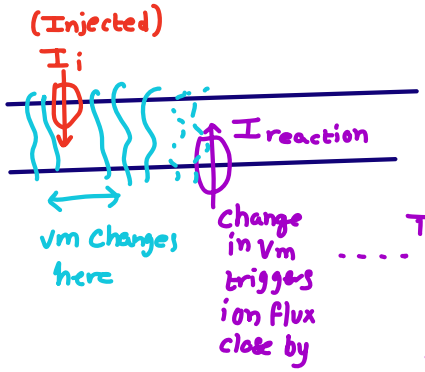
These are minute disturbances in Vm in response to signals. The strength of the stimulus produce a proportional (small) change in membrane potential.

They are decremental. The amplitude of the change in membrane potential attenuates with distance.

e.g. NT at dendrite give a graded potential. We measure near cell body, and at axon hillock.

Also graded potential can have different polarity, if NT cause Na^+ channels to open, Na^+ floods cells making Vm more positive (depolarize); if NT makes K^+ channels open, K^+ leave cells, Vm becomes more −ve (hyperpolarize).

Electrotonic Conduction



This goes on .... so, but with distance, ΔVm decreases

Also depolarize cancel hyperpolarize ←

Graded potentials can be Summed Spatially or temporally.

Spatially: from different neuron

Temporally: ↳ fast interval of firing of 1 neuron.

When a graded potential cause Vm to cross a certain threshold value, some cells are equipped with special proteins to trigger an **Action Potential**

↘ in axon → Graded potential is mainly cell body, dendrites.

Action Potential

I : Graded potential cause Vm to change from −70mV (rest) to −55 mV (threshold)

← Can be from any source that makes Vm more +ve.

II : Crossing threshold cause the activation gate of the voltage gated Na^+ channel to open

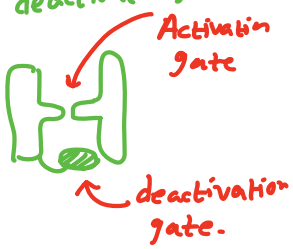
Note : The deactivation gate is also open (as in rest state)

← Na^+ rushes into the cell causing a spike to +30 mV in Vm

↳ Depolarization cause more VG Na^+ gate to open causing more depolarization

↳ +ve feed back loop

→ In rest, activation gate closed deactivation gate open.



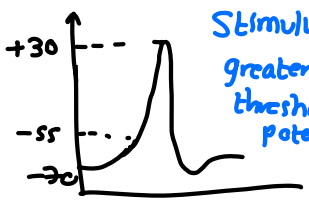
III : 1 ms after opening of activation gate, deactivation gate closes

↘ Stimulus for that is still depolarization but this is a delayed response.

↓ It will remain close until Vm = Vrest

← Na^+ can no longer rush into cell

This stops the +ve feedback loop.



Stimulus must be greater or equal to threshold for action potential.

Greater than threshold cause to increase in action potential.

IV : 1-2 ms after VGNa^+ deactivation gate close, a delayed response to the depolarization cause VG K^+ channels to open

← Increased P_{K^+} and strong gradient of K^+ cause a surge of K^+ to leave cell.

This cause repolarization of the cell.

→ The repolarization acts as −ve feedback to the depolarization which opened VGK^+ channels.

The efflux of K^+ cause the VGK^+ gate to shut.

↓ It overshoots and the cell is hyper polarised as the VGK^+ channel close slowly.

↳ Na^+/K^+ Pump does contribute directly to restoring Vm

TTX block VG Na^+ channel
STX does same
TEA block VGK^+ channel

Leak channels help balance back to Vrest

← Cell is more −ve than should be.

Na^+ leak allow Na^+ to leak in making more +ve

← K^+ leak channels allow K^+ to leak out restoring steady state.

Refractory Period

Stimulus of any strength does nothing

dur. (1–2 ms) **Absolute Refractory**

- Entire depolarization + most repolarization
- Sodium channels are all in use and more stimulus does nothing
- Inactivation gate of $VGNa^+$ closed

The Action Potential Creates a refractory wave.

dur. (5–15 ms) **Relative Refractory**

↳ Increased permeability to K^+

Cancels effect of $VGNa^+$ which just started to open

also, some $VGNa^+$ may still be closed

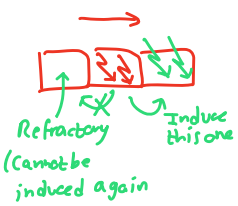
Can make neuron fire again with stronger stimulus.

As relative refractory period proceeds, the stimulus strength required for 2nd fire decreases.

Propagation of Action Potential

An AP does not itself travel down an axon, instead it induces an AP in the neighbourhood until it reaches the terminal axon.

It has an associated polarity



Review Empirical Techniques → Diversity.

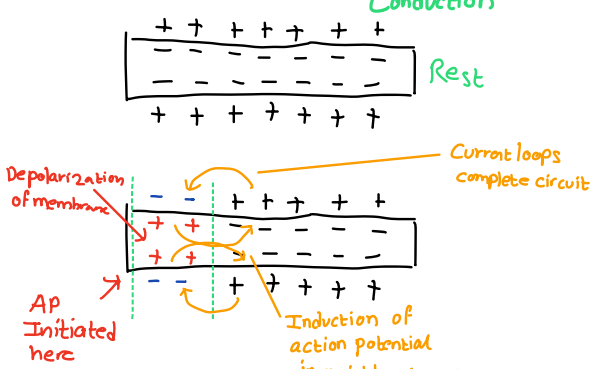
& Molecular Structure of VG Channels.

Selectivity – Pore size

Voltage Sensor.

AP Conduction

Unmyelinated – Continuous Conduction



Nothing happens here despite change in flux as in refractory period. →

↑ Passive conduction

Electrotonically Spread

but unlike graded potential, they do not attenuate as they regenerate along length.

↑ Saltatory Conduction

Myelinated Axons

Length constant (λ), $\lambda = \sqrt{\frac{r_m}{r_a}}$

r_m = membrane resistance

r_a = axial resistance

Decay of signal intensity as it travels:

$V(x) = V_0 e^{-x/\lambda}$

λ = length signal travels to fall to $\frac{1}{e}$ its initial intensity

Greater λ ⇒ Signal can travel longer before same attenuation.

r_a more or less fixed

$\lambda \propto \sqrt{r_m}$

myelination insulates axon and ↑ r_m by making ion flow not possible

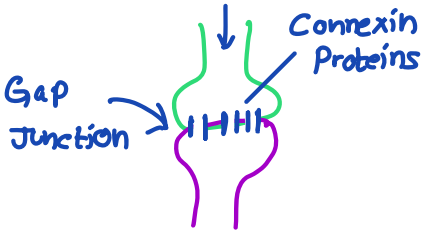
⇒ Signal can travel longer

The next node of Ranvier (where $VGNa^+$ Channel are concentrated) is at a distance just enough for the signal power to trigger another action potential!

Synaptic Transmission

2 Types of Synapses

1) Electric Synapse



Electrical signal generated in one cell is directly transfered to the other cell through ion flow through gap junction. 2° Messengers can also flow.

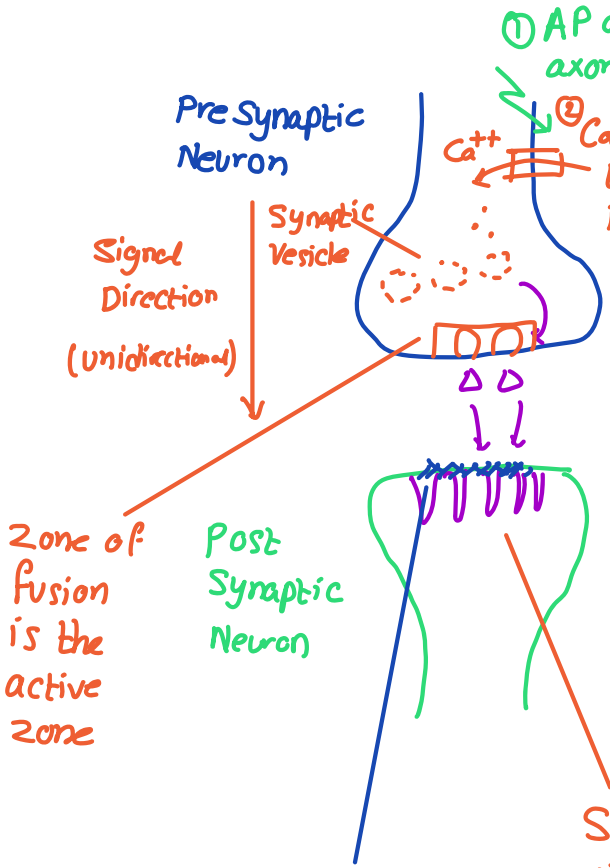
Fast communication *
Bidirectional signal transmission
Can Synchronize electrical activity of cells.

Test: Dye will diffuse through gap junction
Ca^{++} ion has no involvement in Conduction of Signal

* Rectifying (diode) electrical synapse cause unidirectional signal transmission.

* Synaptic delay is the time taken for Ca^{++} to trigger exocytosis

2) Chemical Synapse



What happens to NTs as they reach the post synaptic neuron?

↳ Diffuse & Bind to receptors
↳ Then released from receptors.

→ Taken back in Presynaptic neuron by reuptake proteins / Diffuse away from Synaptic Cleft / Degraded by enzyme or desensitize receptors.

Calcium Dependant Exocytosis

1) Quantal Release (mEPPs)

Vesicles release NT in small packets. Evidence is small spontaneous post synaptic depolarization w/o presynaptic action potential.

Amplitude mEPP ∝ [NT]vesicle

2) Zipper mechanism

SNARE on plasma membrane and Synaptobrevin on vesicle zip together, pulling membrane apart and allowing them to fuse releasing NT.

(Ca^{++} binds to vesicle which change conformation of SNARE complex.)

3) Kiss & Run

The vesicle fuses partially with the membrane, release NT w/o full fusion with membrane and can be recycled.

Useful for high frequency release.

4) Vesicle fuse with membrane.

Clathrin helps recycling vesicle.

It forms a coat on the membrane area and forms a round shape.

Dynamin pinches off the vesicle.

Clathrin coat is removed

Post Synaptic Receptors

Ionotropic

NT binds to the receptor and its pore open to allow ion influx

e.g. Nicotinic AChR

ACh binds to nACh allowing Na^+ & K^+ to move through causing excitation

- usually in
- * down Conc. Gradient
- usually out

Metabotropic

NT binds to receptor It has no ion pore but it activates G-Protein

G-Protein Can activate ion pore

G-Protein Can activate another enzyme Producing 2° Messenger

- Can activate ion pore protein
- Other cellular Processes.

MUSCarinic, mACh Receptors use ACh as NT.

They trigger G-protein which 1) open ion pore

2) Trigger another enzyme releasing 2° messenger.

Excitory Synapse is one that brings V_m of post synaptic neuron close to threshold.

↳ Excitory Post Synaptic Transmission

↳ Graded Potential depending on number of NT

EPSP

- Fast
  - * Ion Channel modulation
- Slow → Longer lasting effects.
  - ↳ 2° Messenger Signalling cascade
    - ↳ Phosphorylate K^+_{leak} → Closing, V_m close E_{Na^+} Depolarization.

Inhibitory Synapse

Synapse that decrease likelihood AP will be generated in Post Synaptic Neuron.

① Hyperpolarize membrane such that it is further from threshold

e.g. NT trigger ionotropic K^+ channel to open causing K^+ to leak out and hyperpolarization.

Inhibitory post synaptic potential can be summed too further hyperpolarizing cells. → Graded Potential.

Decrease in size as they move towards axon hillock

② Stabilise membrane more at V_{rest} so disturbances to membrane potential become less important.

③ Some cells have chloride channels that can be open by NT. Cl^- rush into cell causing hyperpolarization.

Signal Transduction Pathway.

NT

① Trigger G-Protein

Trigger AC, IP_3 (Secondary Messengers)

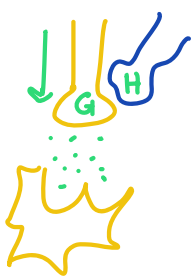
② NT trigger Ligand gated ion channels

③ NT Trigger receptor enzyme

Tyrosine kinase, Serine/Threonine kinase and Guanylate Cyclase.

④ NT trigger intracellular receptors modulating Steroids.

Pre-Synaptic Inhibition



H can control G

if H sends signal to G to decrease transmission to cell body

Manipulation & Exploitation of System

SSRI : Serotonin Reuptake Inhibitor

↳ More serotonin in Synaptic cleft.

Myasthenia Gravis : Decrease AChR activity

Autoantibodies bind to these

α-Bungarotoxin : Block nAChR

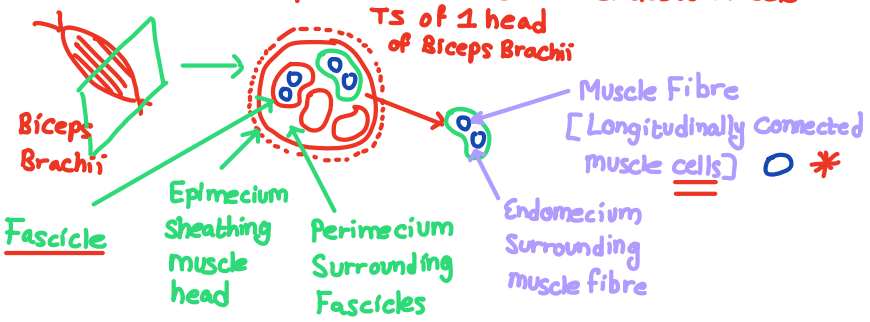
Sarin : Prevent degradation of ACh

α-Latrotoxin (spider) : Affect Ca^{++} metabolism and release of vesicles.

Muscular System

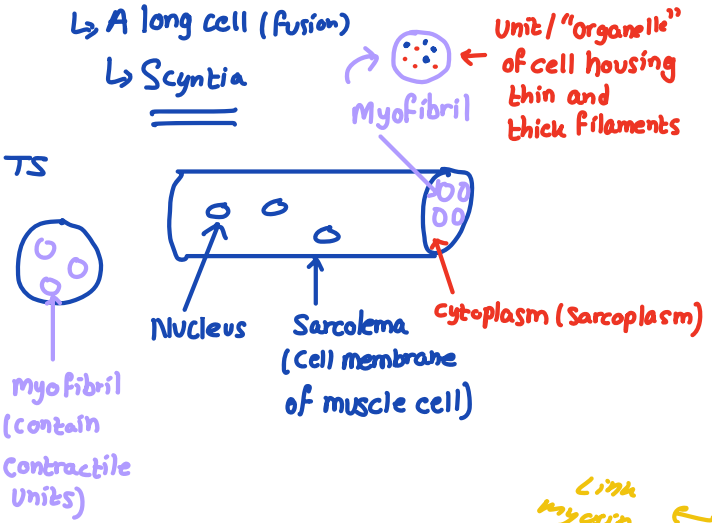
1) Skeletal or Striated Muscles
2) Smooth Muscles
3) Cardiac Muscles

① Structure and Compartmentalization of Skeletal Muscle



② The muscle Cell (fibre)

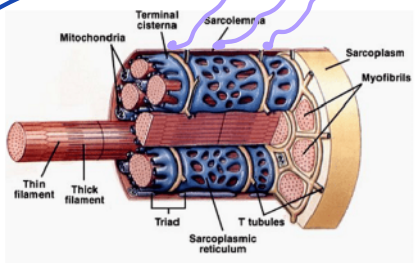
↳ A long cell (fusion)
↳ Scyntia



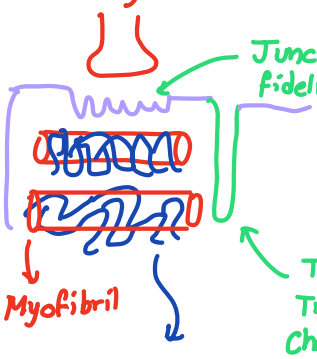
③ Innervation & Microstructure of a muscle cell.

Motor Neuron innervates Surface of muscle cell.

Neuron + fibre = Motor unit

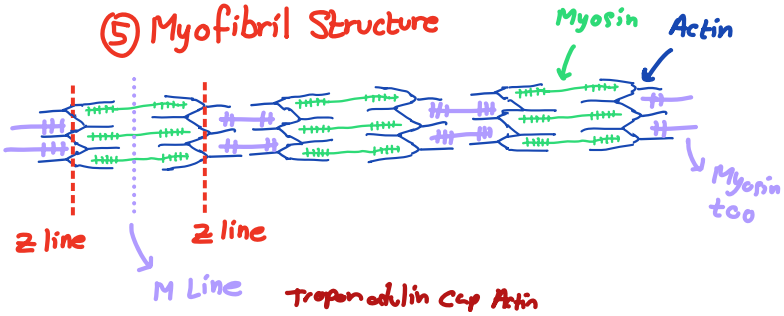


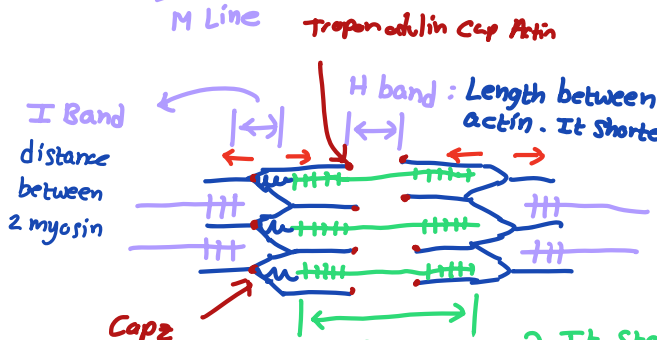
④ NMJ (Neuro Muscular Junction) at Sarcolema.



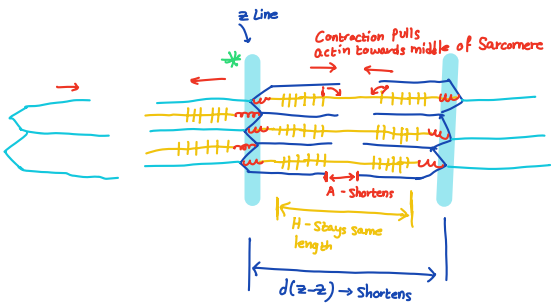
Link myosin toe line ← Titin
Nebulin → organize actin assembly

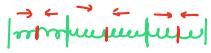
⑤ Myofibril Structure





We See Why H & I Shorten while A remain the same.





WTF!! → The forces Cancel

Sarcomeres have both elastic & Contractile properties
↳ Collective of titin

Excitation Contraction Coupling

What happens?

① Action Potential arrives at terminal axon of PreSynaptic Neuron & Causes the release of NT (ACh)

② ACh (2 need to bind to 5 headed AChR) binds and opens the receptor allowing ions (Na^+) to flow in. ↗ at motor end plate

This causes depolarization in the muscle cell (more +ve). This is known as the end plate potential.

Each quantum vesicle of ACh creates a miniature End plate potential.

This is graded as the number of receptors opening depends on amount of NT released.

Afterwards, same, k^+ channels open restoring V_{rest}.

V_m must climb from −90 to −50 mV. These Sum up to reach threshold and that triggers the opening of Voltage Gated Na^+ channels causing Sudden depolarization and an action potential on the muscle membrane.

This Action moves into the T-tubules (foldings of the membrane) deep into the muscle.

* Inside, it reaches DHP (dihydro pyridine) receptors and cause the receptor to activate. ↗ It also opens to allow entry of Ca^{++} but not enough.

DHPR is coupled to Ryanodine receptor on the Sarcoplasmic Reticulum causing Ca^{++} to flood the cell

Repolarization of Muscle

Without Sustaining AP, the muscle will repolarize, Ryanodine Pump Closes

↓

as $[Ca^{++}]$ decreases

↓

Cross-Bridges Stop forming

↓

Muscle Relaxes

also Ca^{++} ATPase remove ca^{++} to ECM ← NaCaX → 3 Na^+ in cell remove 1 Ca^{++} to cytoplasm

ATPase pump on Sarcoplasmic reticulum remove calcium from cytoplasm back into the SR. } SERCA Protein

Binding of Ca^{++} to calsequestrin (in SR)

decreases the electrochemical contribution of Ca^{++} and makes the work of SERCA easier.

* Excitation dependent Ca^{++} release → DHPR in close apposition with RyR

Ca^{++} dependent Ca^{++} release

↓ DHPR open & some Ca^{++} flood into cell

This increase triggers RyR ↘ In cardiac Muscle

↓ Change in Conformation of DHPR

↗ Trigger RyR In Skeletal muscle

Cross Bridge Cycling

① Set up.

Actin filaments : Ca^{++} binds to T-Troponin. This causes Tropomyosin to change conformation freeing sites for Myosin head to bind.

Meanwhile, Myosin is being primed, it binds with ATP and hydrolyses it to ADP + P_i (Which stay in myosin). This hydrolysis cause the cocking of myosin (energised)

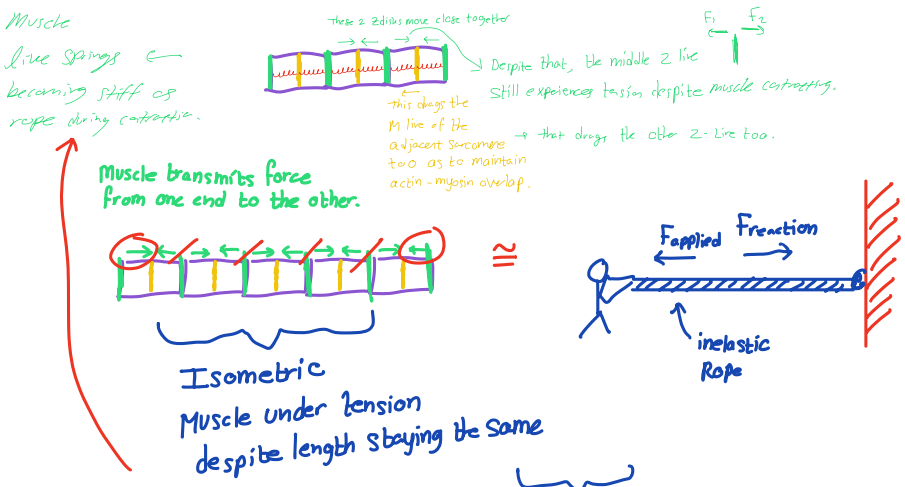
Release from actin. ↑

Myosin can then bind to Actin → Releasing P_i from myosin

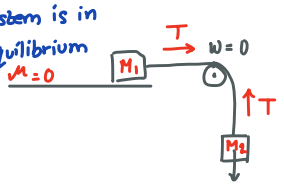
② Power Stroke : Actin is pulled towards middle of Sarcomere.
This causes ADP to leave Myosin

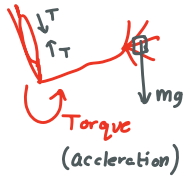
③ Myosin then binds to ATP releasing actin in the process.

ATP hydrolysis again energises myosin and the cycle begins again.



$F_{NET} = 0$ ⇒ System is in equilibrium $a = 0$





System is accelerating & energy is derived from the "wire" itself.

Cellular Motor Proteins.

Provide structural support to cells and hold organelles in place

The Cytoskeleton: Consists of microfilaments, Intermediate filaments, and Microtubules.

Microfilaments

Made of 2 twisted actin filaments.

Actin can polymerize and hydrolyse quickly

→ This allows cells to change shape and move.

- Ameboid movement
- Filopodia are actin-rich cell membrane protrusions that allow cells to sense their environment

Actin filaments also provide support as they thicken the inner edge of the cell membrane providing compressive resistance

Actin acts as track for the movement of myosin.

↳ These interactions allow for:
- Cell Division (cytokinesis)
- Cytoplasmic Streaming
- Muscle contraction

Tropomodulin
Caps actin
Maintains proper length in Sarcomere.

Intermediate Filaments

Microtubules

↓
Tubes made of α-tubulin & β-tubulin.

↳ They too can dissolve and reform quicly.

↳ They help pull chromosomes apart

↳ They are part of flagella & cilia
- Rotating tail movement
- Whipping movement

↳ Act as Centrosome.

Microtubules act as track for the movement of: Kinesin & Dynein

- Kinesin (+): Moves towards cell membrane for exocytosis. They carry vesicles. Away from cell body. (Synthesized NT in Soma) to terminal Bulbs
- Dynein (−): Moves towards inside of cell.

Some NT synthesized in Bouton.

Muscle Action:

Isotonic (Same Tension)
- Concentric → Curl up (Biceps)
- eccentric → Negatives

Isometric (Same length) → Holding weight

Regulation & Modulation of Muscle force.

① Motor unit recruitment.

Smaller tasks recruit smaller motor units at first then proceed to large.

↳ 1 Motor Neuron + Number of fibres it innervates.

Small units are more precise while larger units provide more power

② Biceps & Triceps work in antagonistic pairs.

Need antagonistic because muscle only shorten.

One contracts concentrically while the other contracts eccentrically.

① Delay between AP reaching muscle & contraction.
↳ Calcium and stuff..

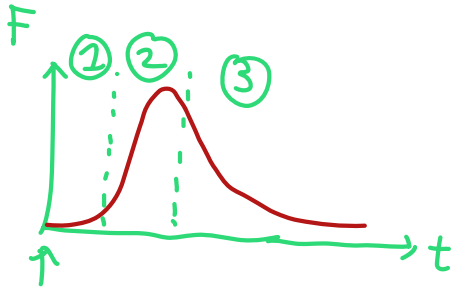
} Latent Period

② Calcium floods

} Sudden acceleration & plateau in contraction

③ Slowly Relaxes

} Time taken for Ca^{++} to be resequestrated



Spatial Summation is 1 motor neuron activating many fibres.

↳ Residual Ca^{++} Theory: Force ∝ $[Ca^{++}]$ in cytoplasm
↳ AP keep firing not allowing $[Ca^{++}]$ to decrease
↳ Summation (temporal)

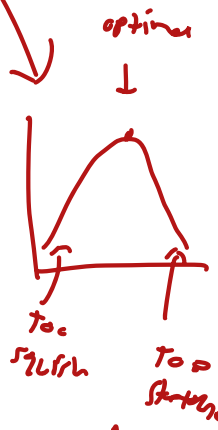
Factors affecting Force of muscle contraction → Only 5% of myosin heads engaged.

↳ Muscle CSA ⇒ More myofibrils in parallel for contraction

Longer cross-bridge length / sarcomere length ⇒ More contraction

↓ Also optimum overlap

↓ Not longer muscles.



Muscle pennation : Greater force for same shortening.

Greater Physiological CSA for same anatomical CSA

↓

Unipennate
bipennate
multipennate
Convergent
Circular
Parallel
Fusiform

Stretch-Shorten cycle

Stretch-Shorten cycle more from rest to near optimal

Regulation

- Myosin - Actin linkage
  - Ca^{2+}
  - Temperature
  - ATP
- Satellite cell hypertrophy...
  - ↓ Actin linkage
  - ↓ PCSA
  - Pennation
- Tetanus
- Motor unit recruitment

Loading muscle to elicit power

↓

Frank-Starling

↳ Thick but for short

↳ This is achieved by volume

more force to eject ↑ blood.

allow for stretch

Muscle Plasticity

Negative regulator of muscle mass ← Myostatin → increase atrophy

Myostatin → Trigger muscle reparation

Hypertrophy

Mechanoreceptors detect microtears and this triggers a cascade to release IGF-2. IGF-2 then binds to a growth hormone receptor on the surface triggering synthesis of muscle proteins

Atrophy

Regulated by: Myostatin, IGF-1, and P13k-Akt-1 Pathway

① When muscle works against load, it secretes IGF-1.

↓

IGF1 trigger P13k which trigger AKT1

↓

Akt 1 Active (Glucocorticoids inhibits activation of Akt1)

↓

Hypertrophy

↓

Increase Protein Synthesis

↓

Increase a.a uptake

↘ Decrease atrophy gene expression

Inactive muscle does not Secrete IGF1

↓

Akt-1 is not Phosphorylated

↓

Akt1 inactive

↓

Atrophy

↓

Increase transcription of atrophy genes

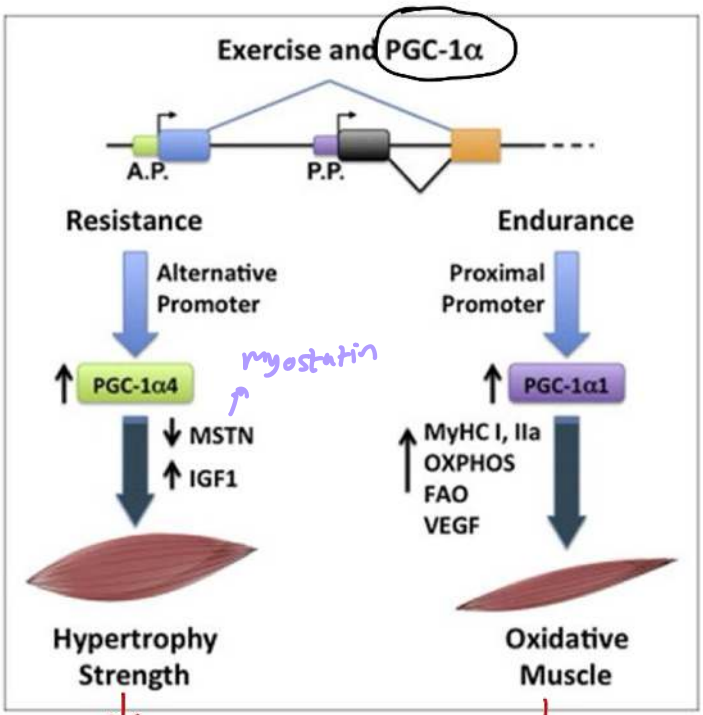
↓

Decrease protein synthesis

↓

Increase protein degradation.

Muscle Phenotype

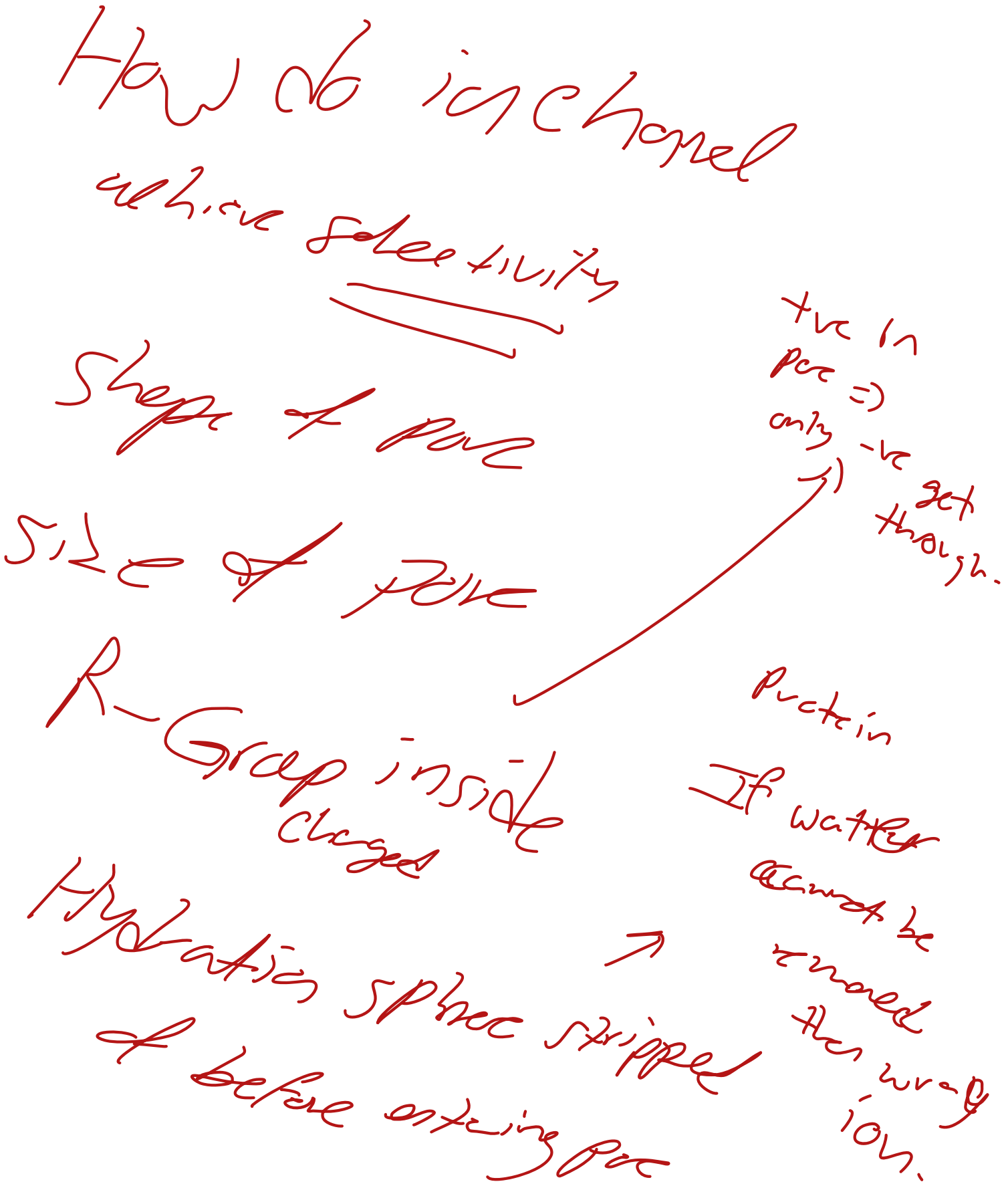


PGC-1α activates PGC1α1 for Endurance ↓ Change way we ATP

Table 6.4 Myosin isoform properties in mammals.

Isoform	Properties
α	This fast cardiac isoform is expressed in cardiac muscle, in species with faster heart rates, or in response to activity.
β (=I)	This slow cardiac/slow oxidative isoform is expressed in cardiac muscle, in species with slower heart rates.
IIa	Found in fast oxidative-glycolytic fibers. ATPase rates intermediate between I and IIx/d.
IIx/d	Found in fast glycolytic fibers. ATPase rates intermediate between IIa and IIb.
IIb	Found in fast glycolytic fibers, this creates the fastest ATPase rates.
Embryonic	Expressed in skeletal muscles in early embryonic development, as well as some adult muscle.
Perinatal	Expressed in skeletal muscles in late embryonic development, as well as some adult muscle.
Extraoccular	Expressed in eye muscles.

more Glycolytic


How do ions choose
achieve selectivity
Shape of pore
Size of pore
R-Group inside
charges
Hydration sphere stripped
& before entering pore
+ve in
pore =>
only -ve get
through.
Protein
If water
cannot be
removed
then wrong
ion.

Review Gating mechanism & Structure of ~~[illegible]~~ Proteins in Channel.

Many ~~[illegible]~~ for ~~[illegible]~~ + Channel

↳ & Subunits

↳ Different ~~[illegible]~~

↳ mechanism

↳ Slight modification of
↳ ↑ Diversity,
Na + Channels
I ge only
↳ Not change
much

Cell Cytoskeleton.

↳ Micro tubules

↳

Muscle attach to bone via tendon.

Bone attach to bone via ligaments.

muscle cell bundle wrapped ← Fascicles ← Bundles within muscle known as fascicle

~~held between~~

~~each other~~

Wrapped by Paramecium

Muscle cell

↳ muscle cells

Stacked longitudinally

TS of muscle we see myofibril.

Muscle cell are multi nucleated

(2) Recognize Cytoskeleton

↳ micro filaments

↳ Actin

(2) Motor Protein

Cargo

→ Walk along microtubule

(3) Pulling on cytoskeleton.

Smooth muscle lines oesophagus, small intestine, stomach lining, Arterial lining

↳ Not under voluntary control

→ Photomicrograph of Cardiac muscle tissue is between smooth & skeletal.

Smooth & Skeletal muscle Contract the same, just organized differently.

Eosin binds to nuclei → blue

Hematoxisin binds to fibres → Pink

Acetyl Choline Biogenesis

Choline + AcCoA —(Acetyl Transferase)→ ACh + CoA

Choline ← Krebs' Cycle

Acetyl Choline Esterase breaks down Ach

Anesthesia
↳ Paralyse muscles for surgery!!

Bungarotoxin α / Same as Curare
Binds to Nicotinic ACh receptors.
Paralysis of Muscles & Paralysis of Diaphragm.

epibatidine
↳ Painkiller...
↓
Small Therapeutic zone...

Deadly Nightshade
↳ Atropine
↳ Competitive Antagonist of Muscarinic Receptor...
↳ Dilated pupils / Increased HR
↳ Increased Parasympathetic NS response

Noradrenaline
↑
NDRI
↳ Dopamine

MAOI
↳ Mono Amine Oxidase Inhibitor
↳ Prevent breakdown of Serotonin

MG → Treat with Neostigmine
↳ ACh Esterase Inhibitor...

Nerve Gas SARIN → Muscarinic Receptor
↳ Cholinergic
↳ Over Excitation of ACh
↳ Paralysis.

Use ATROPINE To treat...

Oximes Reactivate ACh receptors...

Co Release → NT induce both
ionotropic & Metabotropic
Change...

funny Channel → leaky Sodium Channel
↳ Increase funny Channel
Conductance increases HR.

Opposite effect when considering K Channels.

Regulation of HR by activation of
metabotropic Receptors
Slowing heart down via K^+ Channel
Slow Pace of Heart contraction Ca^{++} Channel
ACh return heart from excited back to calm state...

Rest/Digest
Fight/Flight

ACh → Excitory Effect
in Muscle Cells
→ Inhibitory Effect
in Heart Pace Maker Cells

Response of Cell has nothing to do
with the Signalling Molecule...

Muscle Phenotype plasticity.

Glycogen for power output

↑ Myosin atpase

Pathway that lead to specific phenotype.

Age dependent Sarcopenia,
if stay active, body stays healthy.

Blood picks up speed as it returns to heart.

Elasticity of artery acts as pressure reservoir. ↑
↳ Recoil move blood forward.

* Vein not elastic. Can act as volume reservoir.

$I = V/R$

$Q = \Delta P/R$

Batteries ← Reservoir for Voltage

Reservoir for charge

Volume

Total mass of fluid.

Capacitor.

Electrotonic Conduction attenuated with distance.

If passive is equivalent of electric potential difference,

What is volume?

$$I = Qt$$

$$Q = C\Delta V$$

$$P \propto \frac{1}{V}$$

$$V_{ol} = C\Delta p$$

$$V = C\Delta p$$

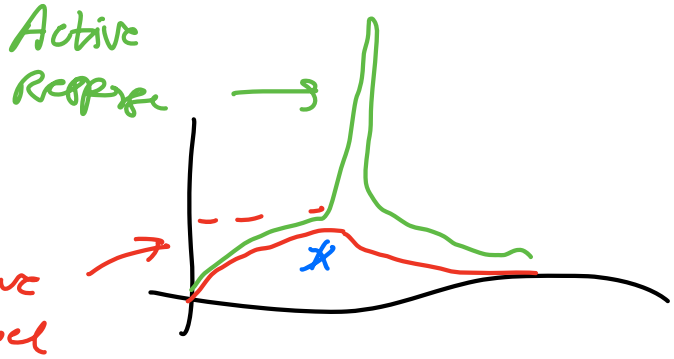
$$Q = C\Delta p$$

$$Q = C\Delta V$$

All cells can conduct electrotonically

But only all cells can produce action potential.

Because have no voltage Na Ca channels.



Active vs passive nerve conduction.

cell

* Sodium Current fast enough to move system beyond equilibrium point.

Cells with short time constant get to threshold quicker.

Muscarinic & Nicotinic Receptors

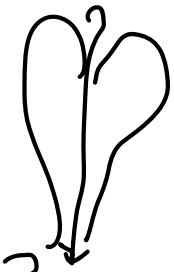
Ach = natural ligand.

nAchR

agonist: Ach

Current: Na^+ goes through

Ionotropic



Protein will convert Na^+ when Ach binds to it

"fast" activity

mAchR

Ach

Nothing goes through the layer activated

Metabotropic

Still needs to bind to Ach but instead of conducting but activating a G-protein

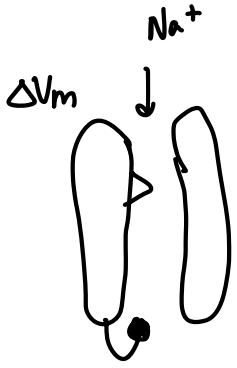
"slow" activity

VG Na^+

no agonist

OX response

Na^+ goes through

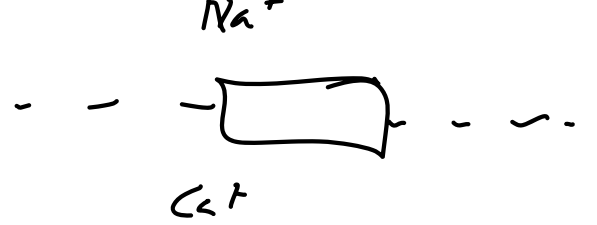


Change in membrane potential cause change in shape.

Equilibrium potential for 1 ion.
Calc. By Nernst equation.

↓

It is the voltage difference across a membrane due to uneven distribution of species across membrane (when system is in equilibrium)



Voltage depend on conc. of Na^+ inside & outside

Is equilibrium potential of sodium dependent only on Na^+

↓

Chemical potential.

↓

Chloride is not permeant across membrane & P = 0

↓

Come to equilibrium because Cl^- cannot cross.

Ions that or not present does not affect equilibrium potential.

Cl^- affect diffusion of Na^+ though.

If no Charge.

The massive effect of ~~Sodium~~ Chloride has no effect across a membrane impermeant to it but its electric effect still persists!

Equilibrium potential electric only??

↳ Yeah.. Voltage...

But in an ion, mass & voltage are together.

Suppose 50mV across ~~total~~

I pump 60 mV

& the system will try to restore balance...

Changing V_m across membrane will change the distribution of ion...

↳ New equilibrium...

Chemical vs Electric Synapse

Chemical

- Synaptic Cleft
  - Dye cannot diffuse
  - Ca^+ needed to trigger vesicle exocytosis
    - Slower conduction.
    - More common
    - But this is also useful
      - Muscarinic receptors can be activated..
    - Can be regulated more efficiently
    - More plasticity → Integration possible → Synapse formation/branching

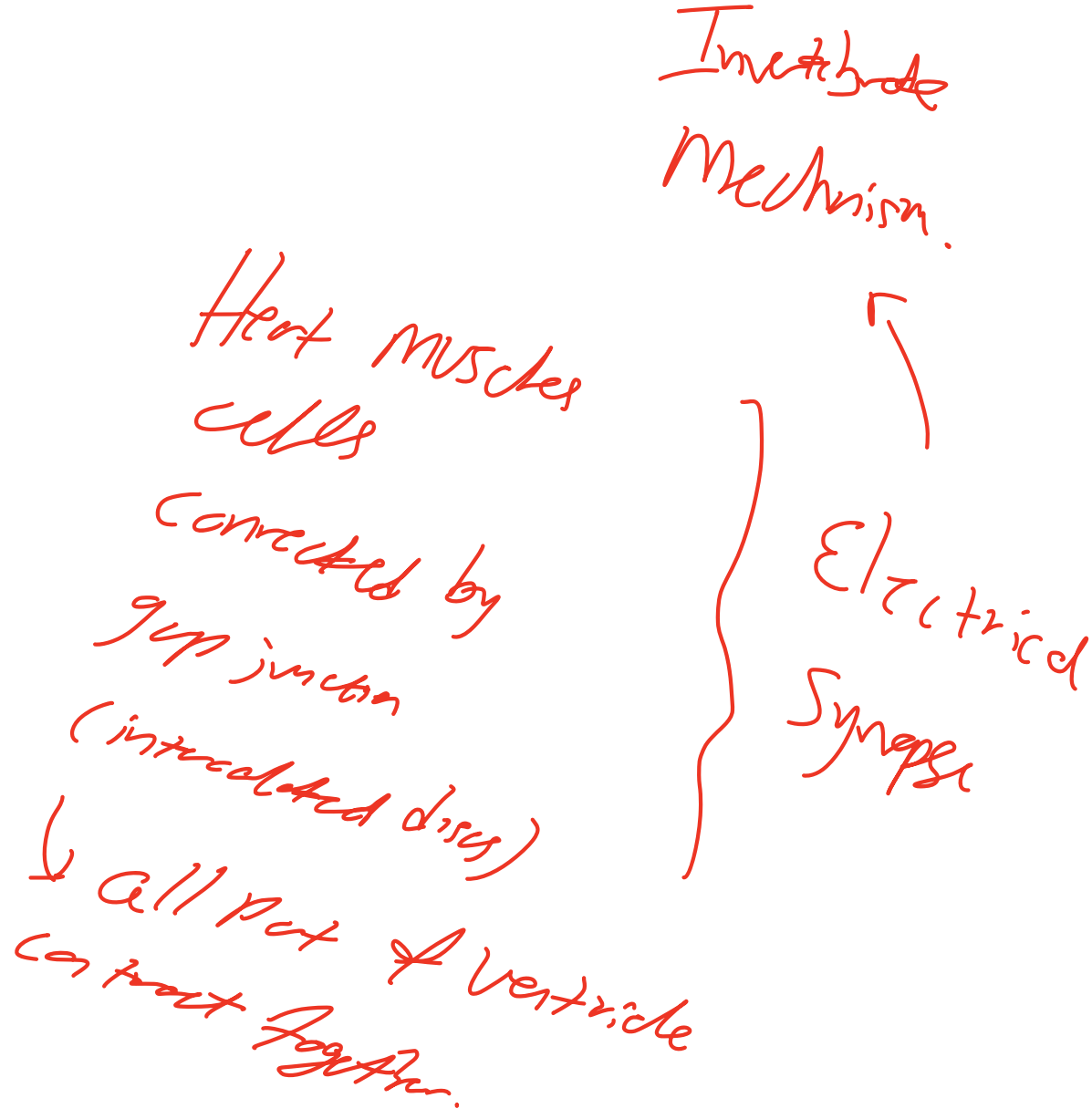
Electric Synapse

- Connexin proteins bound two cells glued together.
  - Electrotonic Con
    - Electrotonic conduction can occur
    - Dye will diffuse through cell
    - Rectifying electrical synapses...
    - Ca^{++} removal has no impact on conduction.
    - Faster conduction
    - Specialized (faster, high fidelity)

Integration

2 neurons act together to bring a third one to threshold

Where none of them alone would be able to do so...


Heart muscles
cells
connected by
gap junction
(intercalated disc)
all part of ventricle
contract together.
Electrical
Synapse
Interbrain
Mechanism.

Right to Left
Shunt

Role of kidney
in regulating
blood volume / blood pH

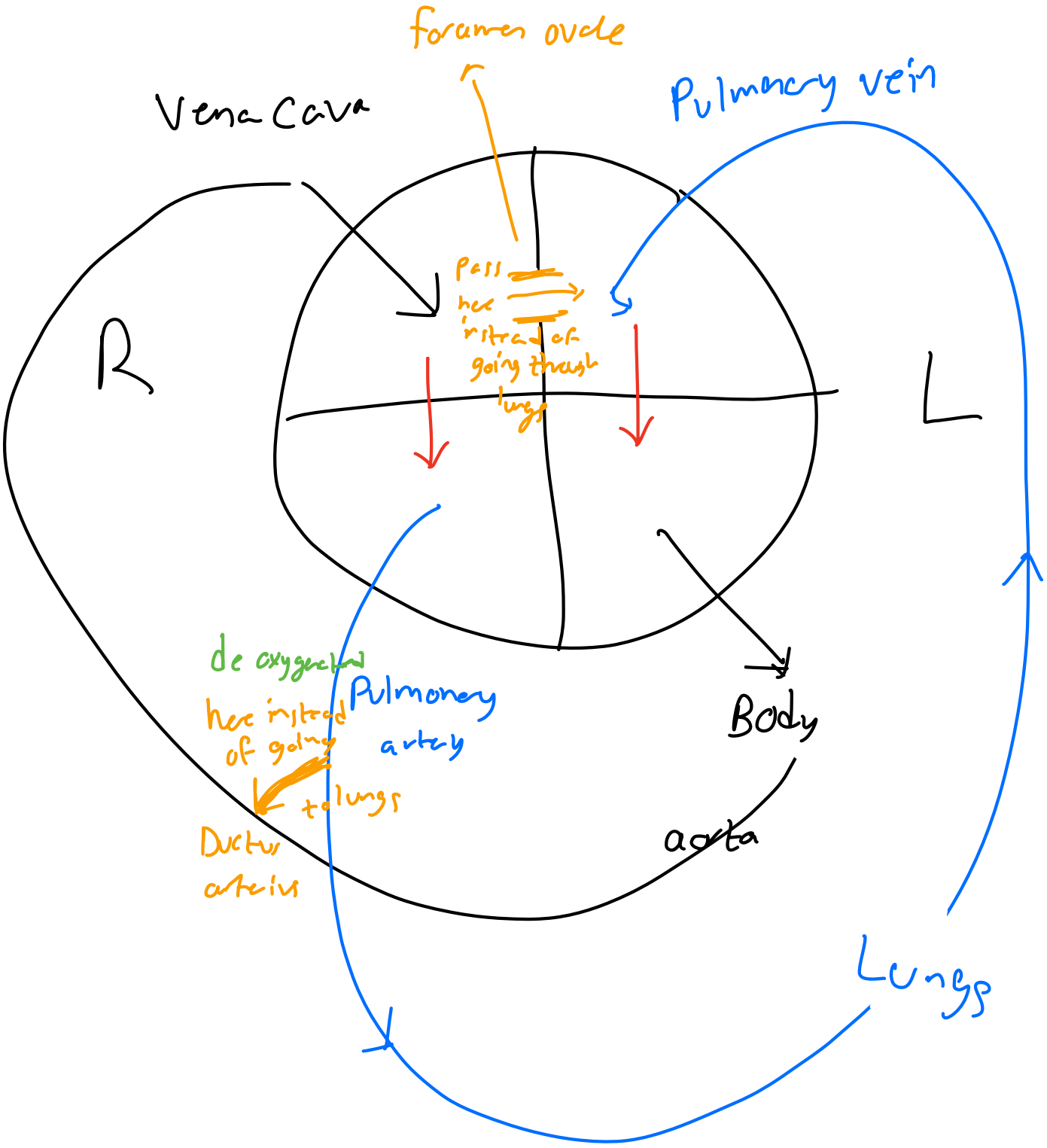
Lymphatic System
Drainage (excess water from tissue fluid)
↳ Disposal (immune response)
Distribution (of fat around body)
↳

Synapse

Muscle

Heart

Lungs



Follow the line.

First breath
close foramen ovale
↳ pressure increase in left atrium
Ductus arteriosus just goes away gradually
↳ ligament

Frank Starling Effect

Max volume of blood in heart

⇒ More distention of heart

⇒ Greater force of contraction.

SNS adjust stroke volume.

The Heart

Why need a circulatory System? → Accessorial → Immune System
Sexual Signalling (e.g. Blushing)
Thermoregulation
Generate force

↓ |→ Small flatworms don't need a circulatory system.

As size increase, diffusion is not enough to sustain organism.

↙ ↓ ↘

Chemical Signalling (hormones)

Waste/ Nutrient Exchange

Gas Exchange

[Mass Transport]

Filtration (Lymph) & ΔPressure from aorta to vein.

Components of a Circulatory System → Create a pressure differential.

- Pump
- Vessel
- Fluid (Blood, Lymph, Hemolymph)

Types of Circulatory Systems

* 1) Open : Insects.

Haemocoel : Cavity providing a defined path for fluid flow

Haemolymph : Its "blood"

↳ Low pressure → Low mass transfer rate.

↳ Tracheal system go deep into tissue for respiration.

Not Swirl around randomly.

↘ Diaphragm assist fluid flow as "pump" & animal body movement also helps.

2) Closed Circulatory System. → There is selective pressure for increased mass transfer → Power Output

↳ Evolved separately from insects.

i) Fish : 2 Chambers but linear heart, 1 Circuit → Body + Gills same circuit. Pressure drop great!

ii) Frogs : 3 Chamber (2A + 1V), 2 Circuits → Body + (Lung/Body for Ventilation) || Still, Oxy & Decxy blood mix.

iii) Turtle : 5 Chamber, 2 Circuits → Body + Lung Separate circuits + Lymph circuit || Ventricle divide into chambers.

iv) Crocodile : Heart completely Divided (Oxy & De oxy not mix), 2 Circuits → One for feeding body, One for Ventilating.

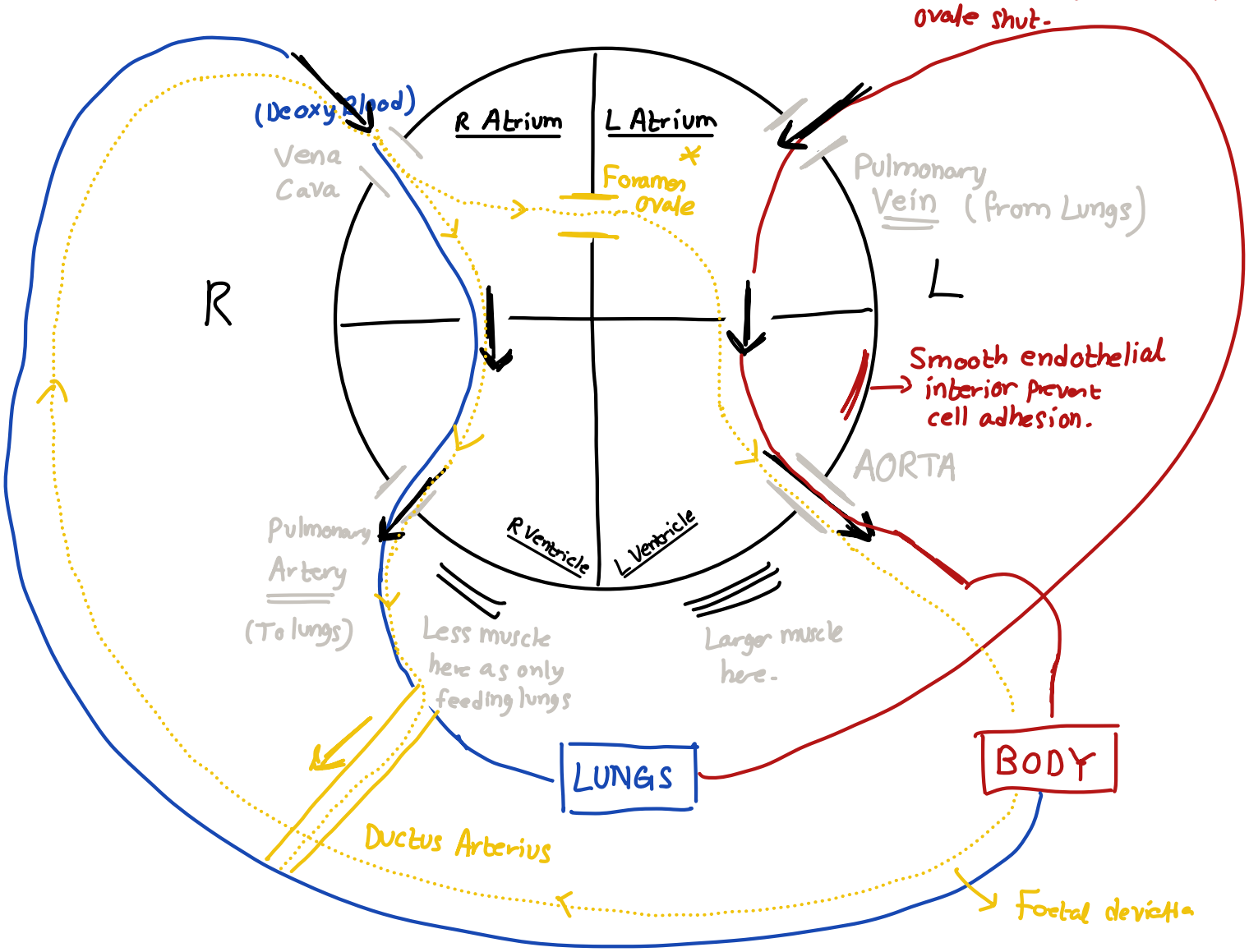
⋮

Birds & Mammals

Human / Foetal / Turtle Heart Schematic

*R-L Shunt

When baby take first breath, lungs draw blood, the return from pulmonary vein force foramen ovale shut.



Foetal Shunting → Bypass blood flow to lungs

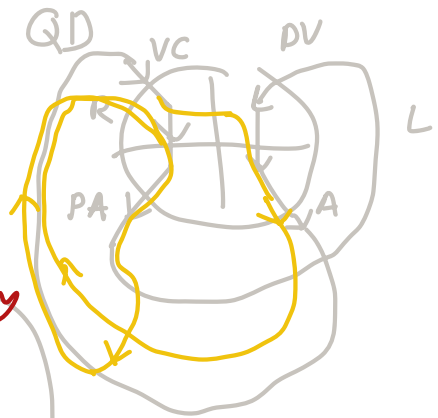
↓

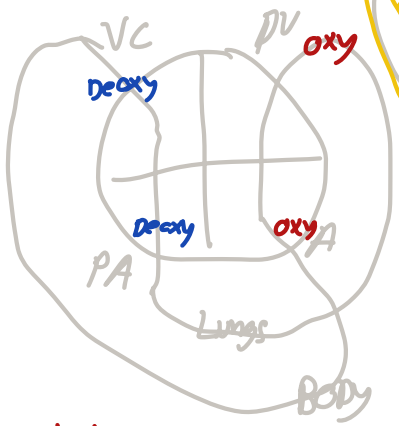
Bypass pulmonary artery feed from vena cava direct to aorta

How? Blood from VC intended for right ventricle then to lungs is sent directly to right ventricle through Foramen ovale.

↑ Not Enough.

Another Shunt from VC/RA to RV and when intended for Pulmonary artery to lungs, intercepted & sent to body.





Mammalian Blood flow circulations : Systemic, Pulmonary, Cardiac

↓ Body ↓ lungs ↳ Feed heart itself.

↳ Coronary artery to myocardium

↳ In fish, it is spongy so blood bathes the myocardium.

Vascular Structure

Heart : Left Ventricle → Greatest Oscillation in Pressure

↓

Artery → High oscillation in pessure due to pulsing of aortic muscle walls helping blood flow

↓

Arterioles → Greatest drop in pessure (ΔP) — Arterioles have tunica media and Capillaries have endothelial cell — Regulation Point of Sending blood to capillaries.

↓

Capillaries

↓

Venules

↓

Vein

Pressure decrease with distance from heart.

↓

Keeps decreasing (No increase)

Largest CSA

Capillaries (Many of them)

Lowest blood velocity in Capillaries due to high CSA.

From Capillaries to Venules/Vein → CSA decrease

CSA ∝ resistance

Just velocity ↓ (Suddenly Velocity goes up)

↳ Pressure still low!

(See the graph again.)

Equations : $Q = \frac{\Delta P}{R}$, $R = \frac{8L\eta}{\pi r^4}$

$Q = \frac{\Delta P \cdot \pi r^4}{8L\eta}$

- ΔP → Vasodilation/Vaso constriction Control
- η → Viscosity blood content
- L → Path Length ↳ Redirection to path of lower length/resistance
- r → Heart Rate or stroke volume

No acceleration

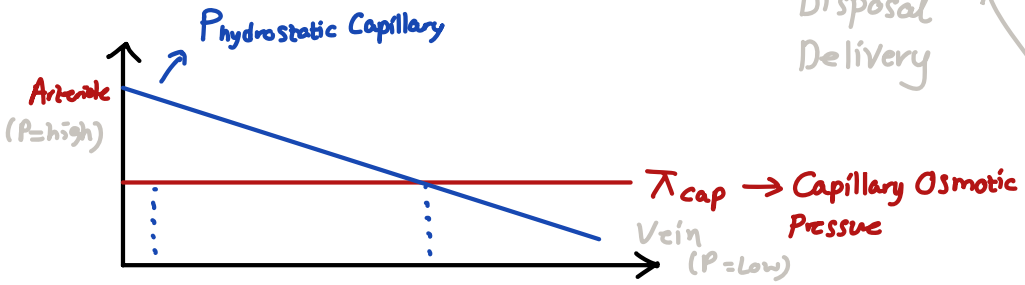
Need Force to provide force to return blood to heart.

↳ Assistance from Skeletal muscle, Breathing muscles (thoracic cavity expansion) Peristalsis

↓

Blood behind Push the blood in front.

Filtration & Reabsorption in Capillaries



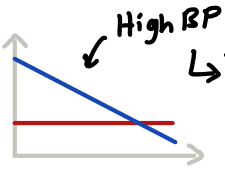
$P_{hyd} > \pi_c$ → Filtration
- ↳ Push stuff out of blood vessel (keep good stuff)

$P_{hyd} = \pi_c$

$P_{hyd} < \pi_c$ → Reabsorbtion
- ↳ Move material back into vessel

Drainage
Disposal
Delivery

Usually more fluid removed than reabsorbed → Blood filtered to keep good stuff
- ↳ Lymphatic System
  - ↳ else accumulate in tissue.



- ↳ Too much stuff removed
  - ↳ Prescribe Diuretic
    - ↳ Pee a lot
      - ↳ Draw more water during reabsorbtion.
        - ↳ ↓ Blood Volume

* Variation in Capillaries

i) Continuous layer
- ↳ For usual conduction & regulation with small molecules that can pass through wall.

ii) Fenestrated in kidneys
Allow larger materials to be filtered at high Pressure

iii) Sinusoidal : Larger things like RBCs in marrow Liver spleen

Low tissue O_2
High CO_2
High Waste → Vasodilation → Lower Resistence → Higher Blood Flow → Increase O_2 tissue, Low O_2, Low waste accumulation

→ve feedback regulation

Arteioles secrete Nitric Oxide responding to vessel damage

Vasopressin / Angiotensin II trigger Vasoconstriction.

Heart Rythm, Conduction & Regulation.

Like squeezing toothpaste at top.
↑

Electric Activity Triggering Contraction

The heart contracts from the apex, upwards → Else useless muscle activity.

Sinoatrial Node (SAN) → Non-Contractile muscle cells with electrical activity.
↳ These fire.

AV Node – Delays the signal while electric activity spread through gap junctions through whole atria.

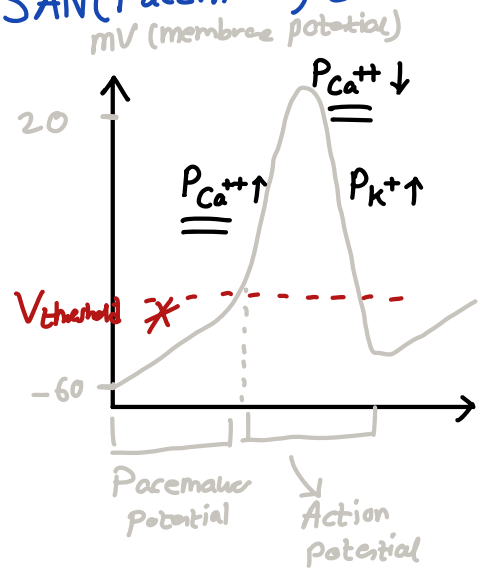
R & L Atria – These contract simultaneously forcing blood to the ventricles. (through internodal pathways)
[Despite the diagram showing it as one path, heart contractions for both circuits occur simultaneously.]

Bundle of His/Purkinje Fibres : Move signal from AV to apex of heart

Ventricle Contraction : This occurs from the apex upwards pushing blood through aorta and pulmonary vein.

Frank Starling Effect : When ventricles fill with blood, the Cardiomyocytes undergo distention making optimal overlap between actin & myosin making more forceful contraction.

SAN (Pacemaker) Electric Activity.



This is a periodic increase to a threshold value that cause action potential to fire.

P_{Na^+} (↑) P_{K^+} (↓)

This periodic drifting up is due to Na^+ leaky funny channel allowing for depolarization

HR ↑ by: Get the faster.

(↑) Permeability funny Na^+ channel

(↓) K^+ Permeability
↳ K^+ leave remain -ve for longer time

↳ Playing with the gradient

↳ Still, K^+ leak out, Na^+ leak in
↳ General Tendency

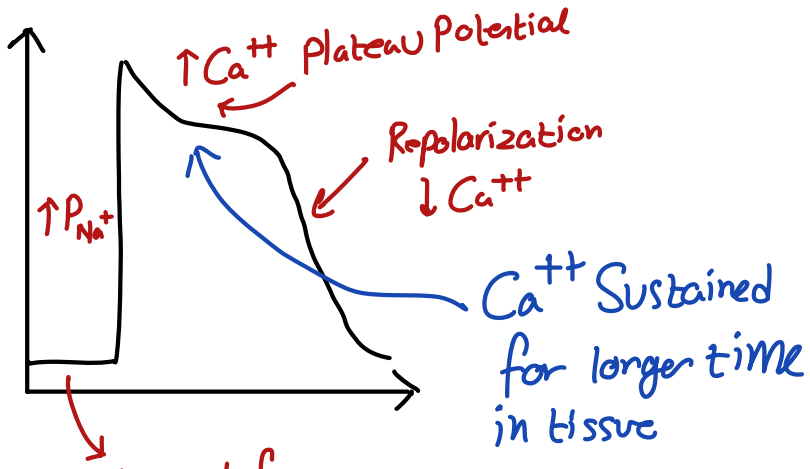
$[Ca^{++}]$ increase during depolarization and decrease during repolarization ↳ RyD closes

DHP trigger RyD release Ca^{++}

$[Ca^{++}]$ ∝ Force of Contraction Needed to do Work

↳ Can Modify force of Contraction by modifying $[Ca^{++}]$. → SV ↑

Other Cardiomyocyte Action Potential.



No need for constantly climbing Sub-threshold potential as this ventricle is under command of SAN.

This Profile Will Vary based on the Membrane channels present.

Also, AV Node peaks slightly later than SAN & Atria showing Sequence of firing.

Bundle of His remain depolarized for a bit longer due to high cytoplasmic Ca^{++}.

Regulation of Heart Activity

Sympathetic (Sympathetic Cardiac Nerve)
(Sympathy for Self-Preservation)

- Increase HR
  - ↓ Noradrenaline/Adrenaline
  - ↓ β-Adrenergic Receptor
  - ↓ G-Protein
  - ↓ ADENYL Cyclase → cAMP
  - Phosphorylate → T-type Ca^{++} channel
  - Na^+ Funny channel
  - Increase rate of depolarization
- Increase Force of Contraction

* In muscle ACh enhances contraction by opening of ionotropic nAChR or Na^+ coupled mAChR.

Parasympathetic (Vagus Nerve)
↓ Acetyl Choline *
↓ mAChR of autorhythmic cells
= ↓ G-protein (Metabotropic)

- Turn off Type-T Ca^{++} channel
  - ↓ less Ca^{++} in Cytoplasm
- Open K^+ leak channels
  - ↓ Decrease rate of depolarization
    - ↓ HR

Other 2° Messenger Pathway

β_1 – Adrenergic receptor

G-Protein → Adenyl Cyclase → cAMP → Protein Kinase

- Protein Kinase → ↑ $[Ca^{++}]$ cytoplasm from ECM by activating L-Type Ca^{++} channel
- Protein Kinase → ↑ $[Ca^{++}]$ cytoplasm from SR Ca^{++} channel phosphorylation.
- Protein Kinase → Also phosphorylate SERCA to remove Ca^{++} faster decreasing relaxation time.
- Protein Kinase → Phosphorylate Myosin Simulating contraction.

↑ End diastolic Volume → ↑ Stroke Volume

↳ More blood filling ventricles during diastole cause Greater ejection of blood (SV). ↳ Frank Starling Effect.

Sympathetic activity makes curve shift upward from basal level.

↳ $y = f(x) \boxed{+C}$

$\Rightarrow y + C$ → Sympathetic activity cause overall increase in Stroke Volume.

↑ Pressure (Body) → kidney ↑ Na^+ Excretion & H_2O
↑ Vasodilation
↑ Contractile Force
↑ HR

↓ Plasma volume
↓ Venous pressure
↓ End diastolic Volume
↓ SV
↓ CO

↓ For same distention of cardiomyocytes by FS Effect, Sympathetic activation increase force of contraction & SV.

Respiration