Introduction to Physiology and Homeostasis (W1)

Human physiology - Homeostasis (L1)

Your body

- Homeostasis: maintenance of static or constant conditions in the internal environment
- Around 37.2 trillion cells
- Amoeba: unicellular organism - need pond with certain conditions to keep them alive
- Multicellular organisms: e.g. 10^{13} human cells - humans can maintain internal environment

Multicellular organism

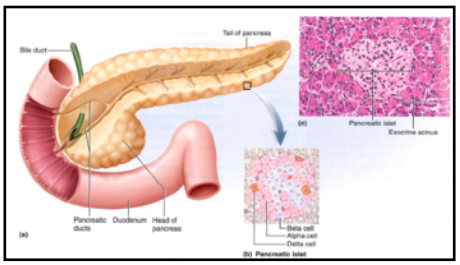
- Cellular specialisation
- **Pluripotent Stem Cells** (PSC)
  - **Mesoderm** (middle layer)
    - Cardiac muscle, skeletal muscle cells, tubule cell of the kidney, RBCs, smooth muscle (gut)
  - **Endoderm** (internal layer)
    - Lung cell (alveolar cell), thyroid cell, pancreatic cell
  - **Ectoderm** (external layer)
    - Skin cells of epidermis, neuron cell, pigment cell

Body's structural hierarchy

- Organism (human)
- Organ system (GI)
- Organ (stomach)
- Tissue
- Cell
- Organelle (mitochondria)
- Macromolecule (DNA)
- Molecule (water)
- Atom

Beta-cells: secretion of insulin (1% of pancreas secretes insulin)

- Pancreatic islet:
  - Beta cell (insulin)
  - Alpha cell (glucagon)
  - Delta cell (somatostatin)
- Bile duct
- Pancreatic duct
- Head of the pancreas
- Exocrine acinus



Multicellular organism

- Specialisation means that **each cell cannot 'know' everything**
- **Interactions among cells** results in **homeostasis**
- Communication is critical
  - Coordinated body activity requires integration of many systems
  - Transmission of information between

Back to our Amoeba in the pond

- Chemical spill, hot spell, acid rain - kills amoeba
- All affect the "bathing medium" of our amoeba

Humans

- Bathing **medium** of cells is the **extracellular fluid (ECF)**
- External environment impacts
  - Amoeba
  - Physiological systems (ECF)
    - Human cell
- Very stable (can define physiology as the maintenance of the ECF)
- Physiology is the maintenance of ECF

ECF normal values (don't memorise - sem 2 we will)

	Normal value	Normal range	Non-lethal limits	Units
PO_2	40	35 - 45	10 - 1000	mmHg
PCO_2	40	35 - 45	5 - 80	mmHg
$[Na^+]$	142	138 - 146	115 - 175	mMol / L
$[K^+]$	4.2	3.8 - 5.0	1.5 - 9.0	mMol / L
$[Ca^{2+}]$	1.2	1.0 - 1.4	0.5 - 2.0	mMol / L
$[Cl^-]$	108	103 - 112	70 - 130	mMol / L
[Glucose]	5.2	3.9 – 7.1	0.8 - 17	mMol / L
Temperature	37	36.5 - 37.5	18 - 43	° C
pH	7.4	7.3 - 7.5	6.9 - 8.0	pH

- PO2: 40mmHg (venous)
- PCO2: 40mmHg
- [Na+] 142mM
- [K+] 4.2mM
- [Ca2+] 1.2mM
- [Cl-] 108mM
- [Glucose] 5.2mM
- Temperature 37°C
- pH 7.4
- We have a normal range, non-lethal limits (some are broad, some narrow) and lethal limits
  - pH non-lethal limit is very tight, glucose has huge range, K+ is tight range
  - K+ above 9mM leads to instantaneous cardiac arrest

ECF Values

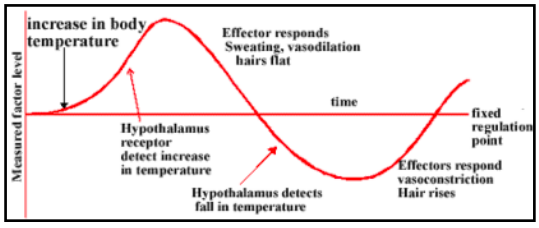
	Hypo-	Normal range	Hyper-
PO_2	hypoxia	35 - 45	hyperoxia
PCO_2	hypocapnia	35 - 45	hypercapnia
$[Na^+]$	hyponatremia	138 - 146	hypernatremia
$[K^+]$	hypokalemia	3.8 - 5.0	hyperkalemia
$[Ca^{2+}]$	hypocalcemia	1.0 - 1.4	hypercalcemia
$[Cl^-]$	hypochloremia	103 - 112	hyperchloremia
[Glucose]	hypoglycemia	3.9 – 7.1	hyperglycemia
Temperature	hypothermia	36.5 - 37.5	hyperthermia
pH	acidosis	7.3 - 7.5	alkalosis

- Hypo- low and Hyper- high
- Low **oxygen**: **hypoxia**; High oxygen: **hyperoxia**
- Low **CO2**: **hypocapnia**; High CO2: **hypercapnia**
- Low **Na+**: **hyponatraemia**; High Na+: **hypernatraemia**
- Low **K+: hypokalaemia**; High K+: **hyperkalaemia**
- Low **Ca2+**: **hypocalcaemia**; High Ca2+: **hypercalcaemia**
- Low **Cl-**: **hypochloraemia**; High Cl-: **hyperchloraemia**
- Low **glucose**: **hypoglycaemia**; High glucose: **hyperglycaemia**
- Low **temp**: **hypothermia**; High temp: **hyperthermia**
- Low **pH**: **acidosis**; High pH: **alkalosis**

Homeostasis

- Maintain a **steady-state dynamic constancy** in a system by **resisting change**
- Maintaining the stability of internal systems depends on ensembles of compensating mechanisms
- Controls systems that operate via **negative feedback**
  - Oppose the direction of change, then switch themselves off
- **Antagonistic arms** of control systems
  - Work against each other to **maintain stability**

Regulation of temperature



- Increase in body temperature
  - **Hypothalamus** receptor detect increase in temperature
  - **Effector responses**: sweating, vasodilation, hairs flat
- Temperature decreases
  - **Hypothalamus** detects fall in temperature
  - **Effectors responses**: vasoconstriction, hair rises
- Fixed regulation point

Control system

1. Some way to **measure** the **regulated variable**
2. Some way to **alter** (effect) the **regulated variable**
3. Something **linking** the two

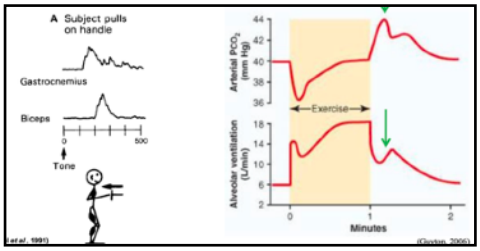
Feedback loop

1. Stimulus
2. Receptor
3. **Afferent** pathway (towards brain "**arriving**"); affect = to influence
4. Integrating centre (brain)
5. **Efferent** pathway (away from brain "**exiting**"); effect = result/consequence
6. Effector
7. Response

Control concepts
- **Negative** feedback
  - Most common
- **Positive** feedback
  - Rare - **non-homeostatic** (increases the instability)
  - Blood clotting, neuronal excitation (both part of negative feedback systems), childbirth
- Require an "error signal" - takes time
- System always playing "catch-up"

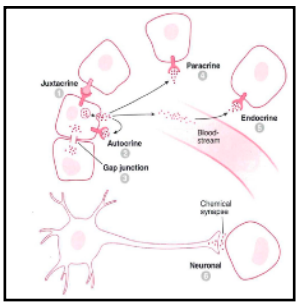
Feed-forward control
- An "**anticipatory**" alteration of effectors - **independent of feedback**
- **Parametric feed-forward** (**adaptive** control)
  - **System 'learns**' (adapts from previous failures)
  - E.g. — ballistic control, **ball throwing**
  - More time you **practise**, the **better your control centre will be**. Not functioning via negative feedback.
- **Predictive homeostasis** (**anticipatory** control)
  - e.g. increasing cardiac function (BP, HR, bronchodilation) in **anticipation of exertion**

Feed-forward control
- **Postural** responses are **triggered centrally before voluntary movements**
  - e.g. subject pulls on handle
  - Before the biceps contract, the **gastrocnemius contracts earlier** for support, and quads - **anticipatory control**
- Exercise increases ventilation (even though Va is controlled by PaCO2 negative feedback)
- **Anticipatory control increases ventilation to ensure there isn't build up of CO2** in exercise
- **CO2 usually goes down because of anticipatory control**
- After finishing exercise, breathing rate goes down, still producing CO2 so increase in CO2 levels in blood - **THEN negative feedback** activates to **increase ventilation and decrease CO2**

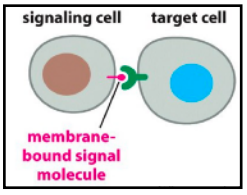


Understanding homeostatic control
1. What is the variable? ([K+], temperature, BP, etc)
2. How do we detect changes in that variable? (Receptor)
3. Where is the decision to act made? (Integrating centre)
4. **How is information passed**? (**Afferent and efferent**)
5. What are the effectors and how do they operate to maintain the regulated variable?
6. How does the negative feedback loop operate?

Cellular communication
- Direct
  - **Juxtacrine** (1) - **physical contact** between cells (membrane bound signal + receptor)
  - **Gap junctions** (3) - **intercellular channels that connect adjacent cells** - share cytoplasm
- Via ECF
  - **Autocrine** (2) - cell releases and takes up the same ligand
  - **Paracrine** (4) - neighbouring cells take up ligand
  - **Endocrine** (5) - via the blood stream to a different site
  - **Neuronal** (6) - chemical synapse
  - **Neuroendocrine**

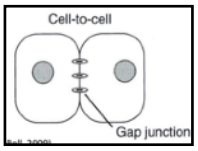


Juxtacrine cell communication
- **Physical contact** between cells involved

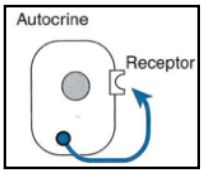


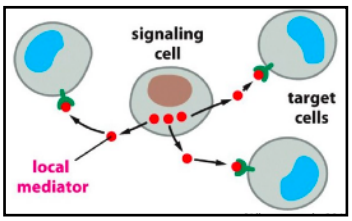
- **Transmembrane proteins and phospholipids**
- Signal cannot diffuse away
  - Notch signalling in neurons

Gap junctions
- Physical contact between cells involved
- Specialised **intercellular connection** directly **connects** the **2 cytoplasms**
- Allows **free passage** for molecules/ions
  - Heart
  - Some smooth muscle

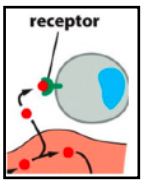


Autocrine cell communication
- Cell signalling to **itself** - immune response
- Signal molecule release into ECF
- Short distances (usually <20μm)
  - **Interleukin-1 (IL-1) in monocytes** (circulate in the blood, not in tissue yet) - hyper activation



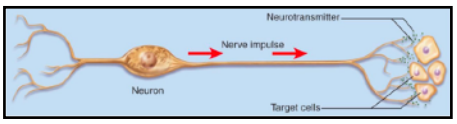


Paracrine cell communication (common)
- Other cells, not in physical contact
- Signal molecule release into **ECF**
- Acts on **nearby cells** - short distances
  - Fgf, Wnt, Hh, TGF-beta

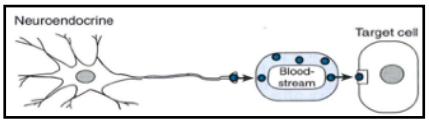


Endocrine communication
- **Long distances**
- Transport via **bloodstream**
- **Hormones** bind to receptor (e.g. insulin)

Neural communication
- **Long distance**
- Target = nerve, muscle and gland
- Noradrenaline, acetylcholine, many other - **neurotransmitters**
- Neuron sends nerve impulse away from soma via axon
- Neurotransmitter released at **synapse** and target cells

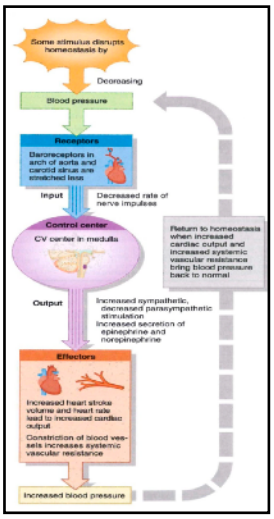


Neuroendocrine communication
- Combined **neural endocrine** signalling
- **Neuron secretes hormones into blood**
- Adrenal medulla (adrenaline) and posterior pituitary (ADH, oxytocin)
  - **Neuron secrete ADH** (pituitary gland) and **enters the bloodstream**. This reaches the **target cell** (kidneys)
- Receive signals from the nervous system and release hormones in response to that signal



Communication
- Most common: neural or endocrine (hormonal) control

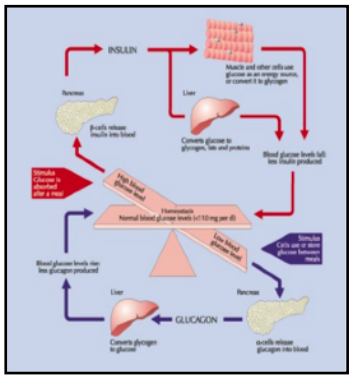
Neural control - baroreceptor reflex
1. Some stimulus disrupts homeostasis
2. **Decrease** in **blood pressure**
3. **Baroreceptors** in **arch of aorta** and **carotid sinus** are **stretched less** (due to low BP)
4. **Decreased rate of nerve impulses** to control centre
5. Nerve signal reaches **cardiovascular centre (CV centre)** in **medulla**
6. Output: **increased sympathetic**, **decreased parasympathetic** stimulation, **increased** secretion of **epinephrine** and **norepinephrine**
7. Effectors: increased **heart stroke volume** and **heart rate** - lead to **increased cardiac output**. **Constriction** of blood vessels **increase systemic vascular**



resistance

8. Increased **blood pressure**
9. Return to homeostasis when increased cardiac output and increased systemic vascular resistance bring blood pressure back to normal

<u>Hormonal control - plasma glucose</u>



- **High** blood glucose
    1. **Beta-cells** release **insulin** into blood by **pancreas**
    2. Insulin effect: **Muscle** and other cells **use glucose** as energy source, or **convert it to glycogen**
    3. Insulin effect: **Liver** converts **glucose to glycogen**, **fats** and **proteins**
    4. Blood **glucose levels fall**: **less insulin produced**
- **Low** blood glucose:
    1. Happens due to stimulus, cells use or store glucose between meals
    2. **Alpha-cells** release **glucagon** into blood by **pancreas**
    3. Glucagon effect: **liver** converts **glycogen to glucose**
    4. Blood **glucose levels rise**: **less glucagon produced**

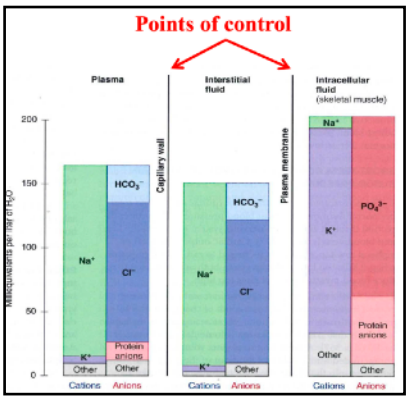
<u>Positive feedback</u>

1. **Head** of foetus **pushes against cervix**
2. **Nerve** impulses from cervix **transmitted to brain** (afferent)
3. Brain stimulates pituitary gland to **secrete oxytocin** (posterior pituitary)
4. **Oxytocin** carried in **bloodstream to uterus**
5. **Oxytocin** stimulates **uterine contractions** and **pushes foetus towards cervix**

- Cycle begins again

Membrane Transport (W2)

Membrane transport (L1)



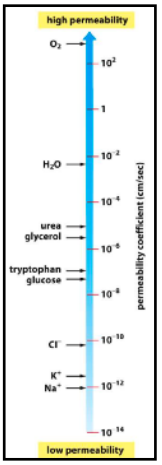
Ionic composition of fluid compartments

- **Plasma**
  - **Mostly Na+ and Cl-**
  - **Low K+**, **low protein anions**
  - HCO3-
- **Interstitial fluid**
  - **Mostly Na+ (dominant) and Cl-**
  - **Low K+, no protein anions**
  - HCO3-
- **Intracellular** fluid (skeletal muscle)
  - **Low Na+**
  - **High K+ (dominant), high PO_4^{3-}**
  - More **protein anions**
- Capillary wall: between plasma and interstitial fluid
- Plasma membrane: between interstitial fluid and intracellular fluid
- **Iso amount of cations and anions inside** and **outside** cell

We can't control simple passive diffusion

- Net flow is downhill - from high to low concentration (down the concentration gradient)
- **Rate of solute movement = PΔC**
  - P = **permeability** coefficient of membrane
  - ΔC = **concentration gradient** across membrane (high for ethanol/water; 0 for ions)
  - Specific for each solute. e.g. ethanol, water (cannot stop movement)

Rate of solute movement = PΔC



P is all about size, solubility and charge

- Solubility = likes dissolve like (membranes are non-polar)
  - Enters the cell very easily
- **High permeability**: **hydrophobic molecules** (O2, CO2, N2, steroid hormones)
- **Moderate permeability**: **small uncharged polar molecules** (H2O, urea, glycerol, NH3)
  - Moderate amount can get through plasma membrane
- **Low permeability**: **large uncharged polar molecules** (glucose, sucrose)
  - Almost 100% rejected and not allowed through plasma membrane
- **No permeability**: **ions** (H+, Na+, HCO3-, K+, Ca2+, Cl-, Mg2+)
  - 100% rejected - require ion channels

C is measures as moles/L (aka M) and is specific to each solute

- Concentration of one ion does not influence concentration of another ion

Water also diffuses down its concentration gradient

- [H2O] water bottle: 55.6mol/L
- [H2O] gatorade: 52.1mol/L
- But we never actually measure [H2O]
- What we measure is **osmolarity**
  - The inverse of [H2O], i.e. - the concentration of **everything other than water**
- **Osmolarity** of water bottle: **0** mOsmol/L
- **Osmolarity** of gatorade: **300**mOsmol/L (isotonic concentration, same as cells)
- So **water will diffuse from low —> high osmolarity**

Osmolarity

- 1 Osmole is one mole of osmotically active stuff (anything except water)
- 1 mole of **glucose** = 1 mole of glucose = **1 Osmole**
- 1 mole **NaCl** = 1 mole Na^+ + 1 mole Cl^- = **2 Osmoles**
- 1 mole **MgCl2** = 1 mole Mg^{2+} + 2 moles Cl^- i.e. **3 Osmoles**
- 1 mole H_2CO_3 = ??? depends on how much it dissociates