The natural universe

Part III: The present – Communication, development and neuroscience

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10. More physiology – communication, circulation, immunity

10.1. The body as communications and control network

The human body is a complicated organism. Its multiple components must maintain coherence in their functioning in order for the whole to work correctly and this requires some form of communication among them. Chemical and electrochemical communications between regions and organs of the body take place constantly.

We have seen examples of communication of information to control reactions:

- reaction products making allosteric bonds so as to inhibit their own production (feedback);
- lactose presence regulating the lac operon;
- insulin and glucagon activating adjustment of blood sugar levels;

as well as direct communication of muscle-control signals by the ANS. Anticipating the last chapter, on neuroscience, we can see communications transporting sensory data input to the brain.

In addition to these communication methods (sense data input, chemical feedback and nervous-system control), another important system exists – hormones, the subject of which constitutes what has long been called the ***endocrine system*** (***ES***), although it is now known that hormones are also produced in organs not uniquely part of the ES.

The nervous system (NS) receives information from sensory organs dispersed throughout the body and in turn transmits information outwards, such as to a particular muscle cell. Communication takes place at speeds on the order of 100 meters/second and so can reach almost any part of the body in less than about 0.01 seconds. The effect of the output, such as a muscular contraction, lasts only a short time, so the action is specific, fast and short-term.

Compared to this, communication by the endocrine system is slower and less specific, but its effects are more durable. Endocrine communication takes place by transmission through the blood or lymph of chemical messengers called ***hormones***. Hormones are ***endogenous*** substances, synthesized within the body by tissues which exist either in specific organs called ***glands*** or in tissues or organs which also have other functions, like the pancreas.

Hormones have an effect only when they encounter cells with special receptors which match (complement) the shape of the hormone. Any such cell may be affected. What happens then depends on the hormone and on the receiving cell. Hormones influence many bodily functions at different levels.

One may imagine a metaphor based on modern telecommunications and good ol' radio. If the nervous system is a high-speed point-to-point link, then the hormonal system is a low-speed broadcast from a point to any stations which may be tuned to that frequency.

Another metaphor is more anthropomorphic. Chemicals which permit communication are like ***messengers*** and that is what they are often called. We will discuss several of them.

Finally, the ES and the NS have the same goal; they work together to optimize functioning of body processes, thus improving the reproductive success of the organism – and the genes.

10.2. Electrochemical communication – the action potential

Cells are surrounded by a membrane composed of a phospholipid bilayer arranged in such a way that the inner and outer membrane surfaces are hydrophilic and the interior hydrophobic. No charged ion, hydrophilic molecule or very large molecule can traverse the membrane. But the cell needs to receive nutriments, expel waste, receive hormonal messages, and so on, so the membrane must not be completely impermeable.

10.2.1. Membrane channels

In order to allow the necessary passage of chemicals, the cell membrane is studded with proteins which control the passage of such objects.

1. ***Ion channels*** are passageways through the cell membrane which allow ions to pass naturally in a direction tending to equalize their electrochemical or concentration gradients inside and outside the cell. Such channels may be ion-specific (for instance, allowing only K^+ ions to pass), charge-specific (allowing either negative or positive ions, but not both) or size-specific. Some ion channels are ***leakage channels***, contributing to the cell's ***resting potential***.
2. ***Gated ion channels*** allow specific ions through the channel on occurrence of a specific electrical (***voltage-gated***), chemical (***ligand-gated***) or mechanical signals. Voltage-gated channels are essential to the formation of action potentials.
3. ***Ion pumps***, especially the sodium-potassium (Na^+-K^+) pump and the calcium pump, run all the time in most animal cells, using energy from ATP to pump ions across the membrane *against* their concentration or electrostatic gradient. They are ***active*** agents, as opposed to passive ion channels which simply allow ions passage,

The concentrations of chemical substances and ions inside and outside the cell generally are not the same and this is crucial to their functioning.

10.2.2. Ion channel structures

Ion channels are composed of at least two ***subunits*** and contain a pore which spans the membrane in order to allow ions to pass. Each subunit is thought to be composed of a number of alpha helices. A change in conformation causes the trans-membrane pore to close. This may happen when the molecule twists and chokes the pore or when a charged region moves and then attracts an oppositely charged flap which closes the channel opening.

Gated ion channels may be of various types depending on the ion allowed to pass and on the circumstances which gate it, *i.e.*, which initiate the passage. The latter property may be of different types:

- ***mechanically-gated***, subject to pressure, for instance, on the surface of the skin or on auditory cilla in the ear;
- temperature-gated;
- ***voltage-gate***d, *i.e.*, sensitive to charged ions;
- ***ligand-gated***, i.e., sensitive to certain molecules (taste, smell, neurons);
- ***photosensitive*** (retina).

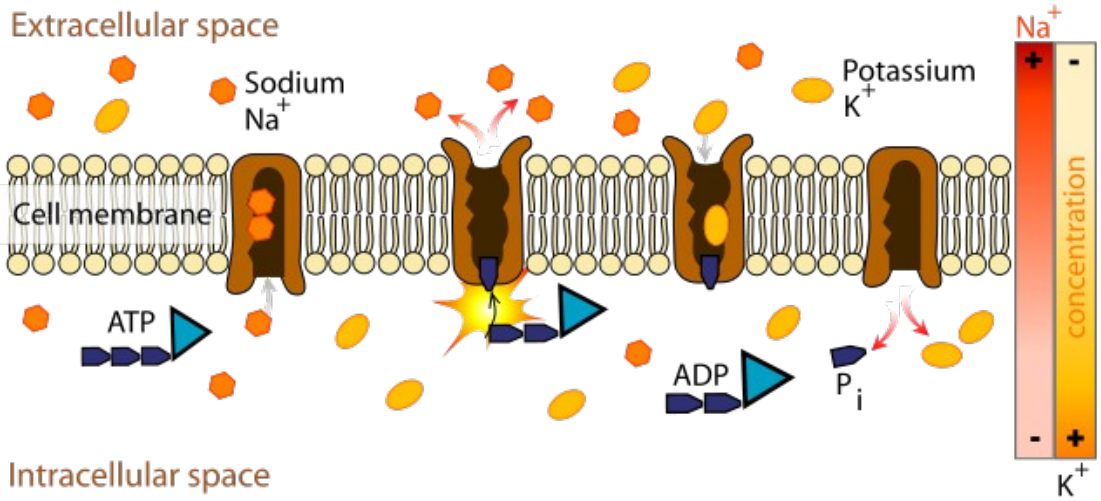
It seems from the latest evidence that all voltage-gated channels in life today are descended from a common ancestor which lived therefore over 1.4 Mya. This is seen from amino-acid sequences conserved through evolution.[1]

1 Kandel (2013), 164.

10.2.3. Membrane potentials and the Na^+-K^+ pump

It all starts with a pump, the ***sodium-potassium*** (***Na^+-K^+***), or ***ATPase***, ***pump***. This object is powered by ATP to flip back and forth between two states and is therefore a form of ***active transport***. In one state, it pumps Na^+ ions out of the cell; in the other, it pumps K^+ ions in. Soon, a concentration gradient is established for each ion, tending to pull the Na^+ back into the cell and to push the K^+ out.

The pump does more than that, because it pushes Na^+ ions out of the cell and pulls K^+ ions in, in a 3-to-2 ratio, so there are three excess Na^+ ions outside for every two excess K^+ ions inside. The result is a net positive potential (electromotive force) for a positive current (flow of positive ions) into the cell and this applies to both ions, since both are positive. Since the pump generates an electric potential, it is said to be ***electrogenic***. Because the extra positive charges outside attract any negative charges inside, they tend to be concentrated close to the membrane surfaces, so the membrane forms an electrical ***capacitance***.



So the result of the pump is triple:

- a Na^+ concentration gradient tending to pull Na^+ back into the cell;
- a K^+ concentration gradient tending to push K^+ out;

an electric potential across the membrane due to the greater number of positive ions outside the cell.Figure 10.1: The Na^+-K^+ pump, by Marianna Ruiz Villareal via Wikimedia Common[2]

Electrical forces are in the same directions for both ions, but chemical (concentration) forces are opposed. Since for Na^+ both are in the same direction, Na^+ ions will flow into the cell until equilibrium is attained, but this can only happen when the electric and chemical forces balance. Since they are of the same sign, this means either that they both reach zero, which is unlikely, or one of them changes sign, and this is what happens. The negative electric potential goes up until it becomes positive and the two forces eventually cancel out. On the other hand, the forces on K^+ are originally in opposite directions and so can balance out when the equilibrium potential is still negative.

Note that there are also lots of large anions, such as phosphate or negatively charged proteins, inside the cell.

Ion channels for K^+ tend to leak K^+. The K^+ tries to follow its concentration gradient out of the cell, but this leaves behind a more negative interior, which attracts it back toward the interior. Eventually, an ***equilibrium*** state is reached where the outward pressure due to the concentration gradient balances the inward pressure due to the electrostatic gradient. Measurements show that the interior has a

2 Image from Wikimedia Commons, en.wikipedia.org/wiki/File:Scheme_sodium-potassium_pump-en.svg.

potential of about -70 mv (relative to the exterior). The cell is said to be ***polarized***. In this state, opening an ion channel would allow positive ions to flow into the cell, ***depolarizing*** it.

If we start over and do the same thing but open a Na^+ channel instead of a K^+, Na^+ enters the cell to decrease its concentration gradient, bringing up the cell's potential until equilibrium is reached between the concentration and electrostatic forces, this time at a measured potential of about +60 mV.

So each ion has an ***equilibrium potential*** which is a function of the concentration difference across the cell membrane. The ***membrane potential*** of the cell as a whole depends on the concentration differences of *all* the ions inside and outside the cell. A very small change in ionic concentration can bring about a much greater change in membrane potential.

Both K^+ and Na^+ leakage channels exist, but leakage through channels is typically 100 times more for K^+ than for Na^+ and brings about a membrane resting potential close to the K^+ equilibrium potential, in the range from -60 mV to -70 mV, the difference being due to a small amount of Na^+ leakage.[3]

In the giant axon of the squid, the following values for equilibrium potentials are found. They are typical for most cells.

Ion type	Equilibrium potential (mV)
K^+	-75
Na^+	+55
Cl^-	-60

10.2.4. Synapses

There are two types of synapses, electrical and chemical. Electrical synapses primarily convey only fast depolarizing signals, whereas chemical synapses – as we shall see – are much more versatile.

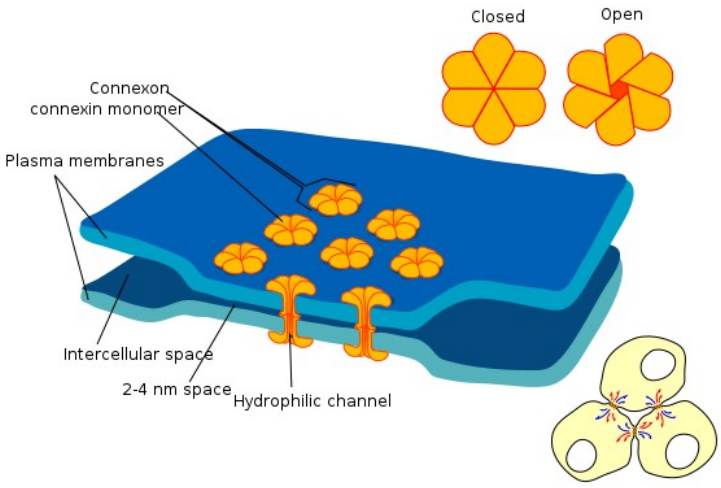


Figure 10.2: Gap junctions, by Mariana Ruiz via Wikimedia Commons[4]

Electrical synapses are also known as ***gap junctions***. They can be qualitatively understood as tunnels between one neuron and another. They are composed of arrays of channels in the cell membranes.

3 Kandel (2013), 101, 127.

4 Wikimedia Commons, https://commons.wikimedia.org/wiki/File:Gap_cell_junction-en.svg..

Each channel consists of two ***hemichannels***, or ***connexons***, one in each of the two communicating cell membranes. The connexons in turn are composed of six subunits called ***connexins***, each of which consists of four alpha helices.

Electric signal transmission in gap junctions is similar to that in axons, ***electrotonic conduction***, passive flow due essentially to the increased K^+ conductance in the wake of the action potential, "pushing" it along.

Some gap junctions are voltage-gated and so conduct current only in one direction, making them ***rectifying synapses***. In some astrocytes (glial cells), Ca^{2+} triggered by neurotransmitters can flow through gap junctions from cell to cell and build up a Ca^{2+} wave. It is not currently certain what the function of such a wave might be.

10.2.5. Receptor channels

There are two types of receptors, depending on whether an ion actually passes through the pore. If the ion does traverse the channel pore and enter the cellular cytoplasm, the channel is said to be ***ionotropic***. If, instead, gating in the extracellular environment sends a signal into the pore, the channel is said to be ***metabotropic***.

Metabotropic channels can be considered as belonging mostly to one of two major families.

- G-protein coupled receptors, and
- receptor tyrosine kinases.

Whereas ionotropic receptors contribute to generating an action potential and act relatively quickly, metabotropic receptors may stimulate any number of actions inside the cell and may begin slowly and have prolonged action.

Members of the G-protein receptor family all follow similar courses. A ligand-gated receptor activates a transducer, often a ***G protein***, inside the cell. The transducer in turn activates a primary effector, which may be an enzyme. The primary effector then produces a second messenger which may activate a secondary effector or have an effect on a target protein. The standard, well-understood example is the cAMP system. In this system, the receptor activates a G protein (the transducer) which activates adenylyl cyclase (the primary effector), which activates the second messenger cyclic AMP (cAMP), which activates the enzyme protein kinase A, or PKA. This liberates PKA catalytic subunits which can go on to phosphorylate substrate proteins. This may lead to a cascade of effects.

G protein subunits can also directly affect ion channels, without the employment of second messengers, opening them or inhibiting their opening. Or they may use second messengers which lead to phosphorylation of a K^+ channel, as in sensitization in *Aplysia*. More in section 11.11.3.

Second-messengers may modulate gene expression, for instance, by modifying histone binding so as to render transcription factors operable. This can lead to a long-term modification of the synapse, over days or weeks.

Synaptic signaling does not always progress in the direction from the presynaptic axon terminal to a post-synaptic dendrite. A G-protein receptor may also activate enzymes which lead to production of a ***membrane-permeable modulator*** which can escape from the receptor and diffuse to the pre-synaptic terminal or to nearby dendritic spines. It may interact with a G protein in a membrane surface or penetrate into the cell where it may have other effects. When acting on the pre-synaptic terminal the modulator is called a ***retrograde messenger*** and brings about ***trans-cellular signaling***.

Receptor tyrosine kinases (***RTK***s), the other major family of metabotropic receptors, are ligand-gated receptors which contain protein kinase domains.[5] They are activated by polypeptides such hormones

5 "A protein domain is a conserved part of a given protein sequence and tertiary structure that can evolve, function, and

such as insulin or various growth factors. Reception of these ligands causes the RTK to auto-phosphorylate, phosphorylation acting as an on-off switch. After activating itself. an RTK can then phosphorylate other enzymes, which promote further cell activity with many possible results, including control of cellular metabolism and regulation of gene transcription.

10.2.6. CNS and muscular receptors

The action brought about by synaptic transmission does not depend on the chemical properties of a neurotransmitter, but on the properties of the post-synaptic receptor.

In the neuro-muscular junction (***NMJ***), tiny branches of CNS axons called ***synaptic boutons*** innervate the ***end plate*** of a muscle cell by emitting the neurotransmitter acetylcholine, ACh. The muscle receptor possesses a relatively large water-filled pore which is therefore permeable to both Na^+ and K^+, as well as other cations, notably Ca^{2+}, but negative charges inside the pore resist passage of anions. So on opening of the channel by ACh, Na^+ ions enter the cell as K^+ ions leave it. The equilibrium membrane potential due to both is about 0 mV. The resulting excitatory post-synaptic potential (EPSP) then activates nearby Na^+ channels and the resulting entrant Na^+ is sufficient to depolarize the cell and produce an action potential, at least in healthy adults.

The ACh receptor has two binding sites for glutamate, both of which must be occupied for the receptor to be efficient. ACh in the synaptic cleft is removed by hydrolysis and by diffusion.[6]

In the CNS, most rapid signaling is done by ionotropic receptors. Receptors in muscle innervation and CNS differ.

	Location	# inputs	transmitter	type	polarity
NMJ	Muscle fiber endplate	1	ACh	ionotropic	excitatory
CNS	Post-synaptic receptor	10^2-10^3	different	ionotropic and metabotropic	excitatory and inhibiting

There are three genetically related families of ligand-gated receptors.

- ACh, GABA and glycine receptor channels are proteins composed of five subunits.
- Glutamate receptors (AMPA, kainate and NMDA) are composed of four subunits.
- ATP (purinergic) receptors are composed of three subunits.

The three types of ionotropic glutamate receptors – AMPA, kainate and NMDA – are so named after the agonists (in addition to glutamate) which activate them.[7] They are always excitatory, or depolarizing. They conduct both Na^+ and K^+, resulting in an equilibrium membrane potential of about 0 mV.

The selectivity of a channel is due to several factors, including the size of the pore and the charge of the pore lining. The latter is due to the dipole nature of the alpha helices, which may be oriented with either their positive or negative ends toward the pore. Ions in solution are surrounded by polar water molecules, ***waters of hydration***, and these may make them too big to cross a channel pore. In some cases though, a charge on the pore may substitute itself for a water molecule, allowing the ion to

exist independently of the rest of the protein chain. ” Wikipedia,, https://en.wikipedia.org/wiki/Protein_domain.

6 Kandel (2013), 193.

7 It is sometimes said that the agonist mimics the proper ligand.

pass. However, detaching the water of hydration takes energy, so the overall process must be energetically favorable from thermodynamic considerations.

NMDA receptors are similar to ACh receptors and are permeable to Na^+ and K^+, but they are permeable to Ca^+ as well. Most importantly, they are normally blocked by an Mg^+ ion, so only when the membrane is depolarized by other receptors, such as AMPA, is the Mg^+ ion expelled by the resulting electrostatic force, allowing K^+ to leave and Na^+ and Ca^+ to enter. Since there are two conditions required for its activation – gating of the receptor and depolarization of the cell– the NMDA channel may be considered a coincidence detector or AND gate.

There also exist slower, metabotropic receptors which can be excitatory or inhibiting.

Although they are in the same family with ACh receptors, GABA and glycine receptors are the common ***inhibiting receptors*** of the CNS. This is because they are permeable to Cl^-, whose equilibrium potential is -70 mV, even more negative than the normal polarized cell potential of -65 mV. When one of these receptors opens, Cl- enters and leads to hyperpolarization of the cell, thus inhibiting any attempt by excitatory receptors to depolarize it.

The large number of inputs in CNS receptors requires integration of these signals. Depending on the relative numbers of excitatory and inhibiting channels, the summed result may be of either sign. The initial portion of the axon has the highest density of Na^+ channels and therefore is most likely to generate an action potential on depolarization of the cell. This region, called the ***trigger zone***, is therefore where integration of the input signals most often is carried out. The summation has two aspects, the effectiveness of which depend on properties of the post-synaptic cell. ***Temporal summation*** takes into account synaptic potentials arriving consecutively in time; ***spatial summation***, potentials arriving on different postsynaptic sites.

The probability that synaptic excitation will produce an action potential therefore depends on the proximity of the synapse to the trigger zone. Although they may arrive anywhere on the cell, the most common are axodendritic (emitter axon to receptor dendrite), axosomatic (axon to cell soma) and axo-axonic (axon to axon). Be that as it my, almost 95% of all signals in the brain arrive on tiny processes on dendrites called ***dendritic spines***. The narrow necks of spines inhibit diffusion of molecules from the spine and so, for instance, Ca^{2+} from NMDA receptors can build up locally. Any back-propagating signal from elsewhere in the neuron can then add to that in the spine, opening more NMDA channels and letting In more Ca^{2+}. In this manner, the spine can detect simultaneity of presynaptic and back-propagating signals and this may play a role in memory storage.[8]

10.2.7. Neurotransmitters

So far, the neurotransmitters to which we have referred have been substances released from vesicles in presynaptic terminals by Ca^{2+}-induced exocytosis to cross the synapse and activate (or inhibit) a post-synaptic terminal. There are other sorts of neurotransmitter, though, such as those ejected directly from a cell's cytoplasm. In general, the definition of neurotransmitter is imprecise, but that need not concern us overly much.

In the CNS, there are two principal types or classes of signaling substances:

- small-molecule transmitters, such as ACh, dopamine, glutamate, GABA and other, most of which, in order to keep up with demand, are synthesized locally at the terminal;
- neuroactive peptides (short amino-acid polymers), such as oxytocin, vasopressin, melatonin and insulin, which are synthesized in the body of the cell.[9]

Several peptides may be produced from the same genetic precursor by cleaving different parts of the

8 Kandel (2013)< 231.

9 Kandel (2013), 305.

molecule. Many of these peptides also serve as hormones.

In order to avoid accumulation of neurotransmitter molecules in the synapse and also to terminate the synaptic action, these molecules must be reabsorbed by neurons and glial cells. This active ***reuptake*** is somewhat similar to the process in which neurotransmitter molecules are loaded into emptied vesicles and the two together form a cycle of neurotransmitter release, reuptake and reuse. Both use ATP to power pumps to establish a potential gradient, the energy of which is then used to drive the neurotransmitter molecules across the membrane, either from the synaptic cleft into the terminal or from the cytoplasm into the vesicle. The greatest difference between the two processes is that vesicle loading uses a proton pump to create an H^+ electro-chemical gradient, whereas reuptake establishes and uses a gradient of Na^+ ions.[10] Some GABA and most glutamate is taken up by nearby glial cells, converted to glutamine and transported to the terminal where it is reconverted and loaded into vesicles.

10.2.8. The action potential

Consider a polarized nerve or muscle cell at rest, with a membrane potential of around -70 mV. Suppose something happens which causes the membrane potential to increase (i.e., to become less negative). This could be due to entry of ions through a ligand-gated channel (as in neurons) or a mechanically-gated channel (as in a somatosensory channel) or simply due to K^+ leakage (as in a pacemaker cell of the heart). If the increase is small, nothing happens. But if it becomes sufficient to bring the potential up to the ***threshold*** value of -55 mV, then a voltage-gated Na^+ channel opens, allowing Na^+ to come rushing into the cell, quickly raising the potential to a positive value and depolarizing the cell. When the potential reaches 30 mV, the voltage-gated Na^+ channels close but voltage-gated K^+ channels open and K^+ starts rushing out of the cell, bringing the potential back down (positive charges are leaving the cell) and ***repolarizing*** it. Note that once the threshold potential is achieved, the action potential will happen. This is the ***all-or-nothing*** aspect of aspect potentials. Cells can also [WHAT??]

10 Kandel (2013), 304.

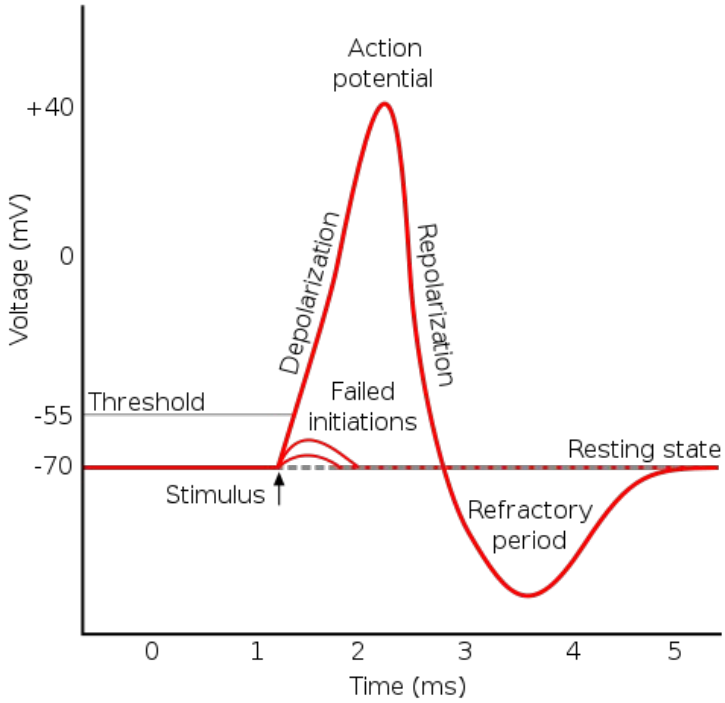


Figure 10.3: Action potential, from Wikimedia Commons

In muscles, release of the neurotransmitter acetylcholine (ACh) by motor nerves opens ligand-gated channels which allow the cell to depolarize to the threshold for voltage-gated sodium channels. The resulting action potential eventually opens another channel which allows Ca^{++} into the cell. The Ca^{++} binds to troponin in the muscle fiber and unlocks it, so that myosin heads can "walk" along the thin filament and contract the muscle.

The heart is special in that it initiates its own action potentials in a repeated, periodic way. The cycle is initiated not by a ligand-gated channel, but mostly by leakage channels which allow some Na^{+} to enter the heart, gradually raising the membrane potential from about -60 mV to -40 mV. This is the threshold value for a gated Ca-ion channel to open, allowing depolarization of the cell as Ca^{++} ions enter. After about 100-150 milliseconds, the Ca^{++} channels close and K^{+} channels open. As K^{+} rushes out of the cell, the potential re-descends to a bit under its initial resting value. Then the K^{+} channels also close and the cycle starts over.

10.2.9. The cell as electric circuit

A cell membrane contains channels, such as leaky channels, permeable to ions. An ion within a cellSecond-messengers may modulate gene expression, for instance, by modifying histone binding so as to render transcription factors operable. membrane is subject to two forces:

- a chemical force due to its concentration gradient;
- an electrical force due to the electric potential difference across the cell membrane.

At some degree of of diffusion, the two will balance and the ion will have attained its equilibrium potential. Based on thermodynamic principles, the ***Nernst equation*** gives this equilibrium potential

$$E_x = \frac{RT}{zF} ln \frac{[X]_o}{[X]_i},$$

where $[X]_o$ and $[X]_i$ are the concentrations of the ion outside and inside the cell. (R = gas constant, T = temperature in Kelvin, z = ion valence and F = Faraday constant.)

Note that, for a positive ion with z=+1, the ln term is negative if the concentration is greater inside the cell (the K^+ case) and positive if the concentration is greater outside the cell (Na^+).

The Na^+-K^+ pump causes the positive ion K^+, with z=+1, to be more concentrated inside the cell, so the log term is negative, as is the equilibrium potential for K^+. Na^+ also has z=+1, but is more concentrated outside the cell, so its equilibrium potential is positive. Since current is by convention the direction of flow of positive charges, the resultant current for K^+ is out of the cell; for Na^+, into it.

Taking into account multiple ions leads to the Goldman equation, in terms of the permeability P_i of the cell membrane for each ion. For three ions, th overall cell membrane potential is

$$V_m = \frac{RT}{F} ln \frac{P_K[K^+]_o + P_{Na}[Na^+]_o + P_{Cl}[Cl^-]_o}{P_K[K^+]_i + P_{Na}[Na^+]_i + P_{Cl}[Cl^-]_i}.$$

The permeability depends on the number of ion channels open for the ion in question. Many channels for one ion type compared to the others would push the resultant V_m toward the equilibrium potential for that ion. For most neurons, the cell membrane is about -65 mV, close to the K^+ equilibrium potential.

Following the enormously successful Hodgkin-Huxley model, one can consider the cell as composed of an electric circuit with the following components.

Following the enormously successful Hodgkin-Huxley model, one can consider the cell as composed of an electric circuit with the following components.

An channel can be open or closed (or somewhere in between) and so can be represented by an electrical resistance. Biologists prefer to speak in terms of of the conductance, the inverse of the resistance. So the electric force of a single-ion channel is represented by a ***conductance*** and this is in series with a ***battery*** of emf equal to the equilibrium potential of the ion given by the Nernst equation. Note that an ion channel must be represented by a conductance and a battery for each type of ion it lets past.

Because of concentration gradients set up by the Na^+-K^+ pump, the cell membrane has charges adhering to both its cytoplasmic and extracellular sides and the membrane therefore acts like a ***capacitor***.

A pump, such as the Na^+-K^+ pump, acts as a ***current generator***.

The cell-membrane capacitance is given in terms of the charge on the cell by

$$C = \frac{Q}{V},$$

so the current

$$I = \frac{dQ}{dt} = C\frac{dV}{dt}.$$

From Ohm's law in conductance form

$$V = IR = \frac{I}{g},$$

or

$$I = gV.$$

The ***convention*** used is that a positive current is a flow of positive charges from within the cell to without. The equilibrium potential for K^+ is negative, so the current due to that alone must be $-g_K E_K$. Note that for Na^+, this leads to a positive current into the cell. Taking the membrane potential into account leads to the current due to the electrochemical driving force on ion I

$$I_i = g_i(V_m - E_i)$$

where V_m is the membrane potential and E_i the equilibrium potential of the ion. Note that the current is positive when a positive ion flows out from the cell. The term $(V_m - E_i)$ is called the ***electrochemical driving force***.

We can then the laws of electric circuits which say that (a) the sum of the currents at a point in the circuit must be zero in order to conserve charge; and (b) the sum of voltage differences around a closed circuit must be zero. This gives, for one ion channel for one ion I of resistance R_i, conductance g_i and capacitanceC_i in series with a source of emf $\mathcal{E}$

$$\mathcal{E} - I_i R_i - QC_i = 0.$$

This can be solved to show the current's time evolution due to the presence of the capacitance.

In these terms, we can also describe the events of the generation of an action potential (AP).[11] We start with an excess of Na^+ ions outside the cell and of K^+ ions inside, but unbalanced, with three Na^+ to each K^+ (above the background concentrations). So...

- The cell membrane capacitance is charged with positive charges on the extracellular side and negative on the cytoplasmic; and
- a chemical concentration gradient exists for each of the two ions, trying to push Na^+ in and K^+ out.

When ligand-gated channels open to let Na^+ enter the cell, the effect is to increase the conductance of the Na^+ channel.

- This contributes to depolarization of the membrane capacitance, which
- causes other Na^+ channels to open, further increasing Na^+ conductance and further depolarizing the cell capacitance.
- The membrane capacitance is now pushed towards E_{Na} and this generates the rising phase of the AP.
- But depolarization starts to close Na^+ channels, decreasing Na+ conductance.
- Somewhat later, the depolarization starts to open K^+ channels, increasing K^+ conductance.
- The resulting outflow of K^+ ions re-polarizes the membrane and starts the descending phase of The the AP. The membrane potential actually descends below its resting value before all the K^+ channels have time to close, but then come back up to the resting potential.

10.3. The endocrine system – hormones

The endocrine system, consisting of all hormone-synthesizing tissue, works together with the nervous system to regulate bodily processes. As already pointed out, hormones are far more numerous than those only produced by glands. Also, some substances, such as norepinephrine, function sometimes as hormones, sometimes as neurotransmitters.

Hormones are of four types:

- ***lipid hormones*** – made from fatty acids; the primary ones, ***steroid hormones*** like estrogen, testosterone or cortisol, are derived from cholesterol;
- ***peptide*** (***protein***) ***hormones*** – made of short chains of amino acids; include anti-diuretic hormone (ADH), oxytocin and insulin;
- ***glycoprotein hormones*** – made of longer chains of amino acids with carbohydrate side-chains;

11 Kandel (2013), 156-7.

includes thyroid-stimulating hormone (TSH);

- ***amine hormones*** – synthesized by modification of amino acids tryptophan or tyrosine; examples are melatonin, thyroid hormones, epinephrine and norepinophrine, and dopamine.

Like other polypeptides, peptide and protein hormones are synthesized through gene expression.

Hormones are secreted in response to three sorts of stimuli.

- ***Humoral*** stimuli are due to changes in blood concentration of substances which are not hormones, such as when high blood sugar causes the pancreas to secrete insulin.
- ***Hormonal*** stimuli are exactly that, hormones which bring about the release of other hormones, as when the hypothalamus emits releasing hormones to signal other glands to secrete their hormones.
- ***Neural*** stimuli occur when the nervous system directly initiates hormone secretion, an example being when the sympathetic nervous system initiates the fight-or-flight response.

In order to have an effect, hormones must activate specific receptors on cells. A cell's receptivity depends on the number of receptors on the cell and this can vary with time (***up-*** or ***down-regulation***) in response to too few or too many hormones in the blood stream, an example of the feedback control of hormone concentration.

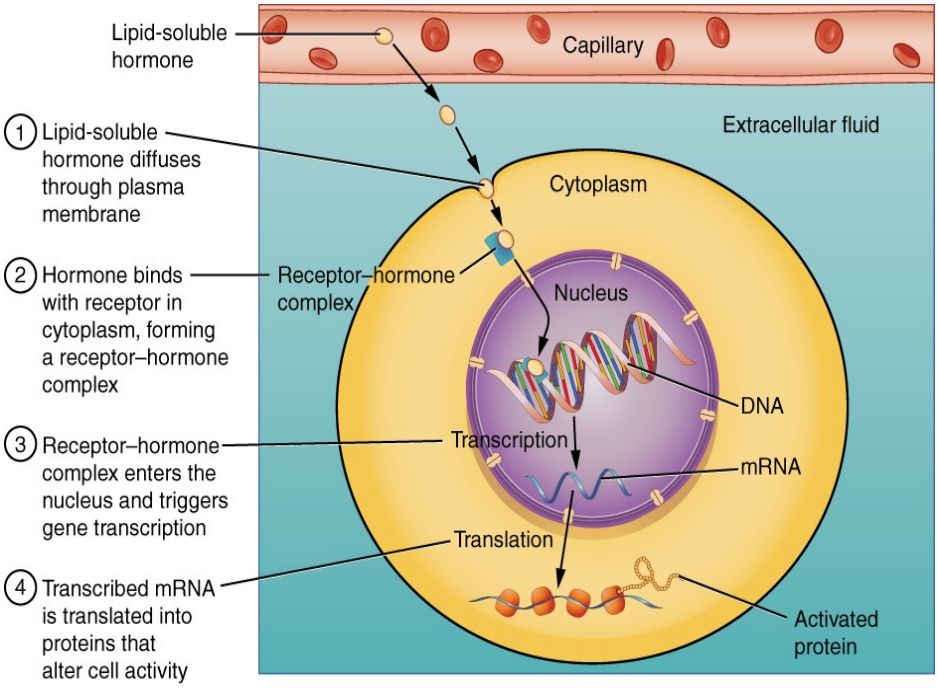


Figure 10.4: Binding of lipid-soluble hormones, from Openstax College[12]

Reception can happen in two ways. Lipid hormones are hydrophobic and therefore capable of crossing cell membranes, whereas the other three types can not. But since blood is water-based, lipid hormones must bind with a transport protein in order to travel through it. This procedure significantly increases the lifetime of the lipid-transport complex. Lipid hormones cross the cell membrane into the cytoplasm where they bind with a receptor in the cytoplasm. The receptor-hormone complex moves into the nucleus and activates (regulates) the expression of an appropriate gene to manufacture a protein which should lead to the desired result.

The other three types, ***non-steroid*** hormones (called ***first messengers***, in this case), can travel freely

12 http://cnx.org/contents/FPtK1zmh@8.24:CTrkWxyU@3/Hormones.

through the blood, but cannot cross the cell membrane and so must bind with a receptor on the outside surface of the membrane. This begins a cascade of signals. A G protein is activated which in turn excites the so-called ***second messenger*** (usually cAMP[13]). Some steps later, a protein is activated by ***phosphorylation*** (addition of a phosphoryl radical) and this may lead to a cascade of many different effects, including synthesis of other products.

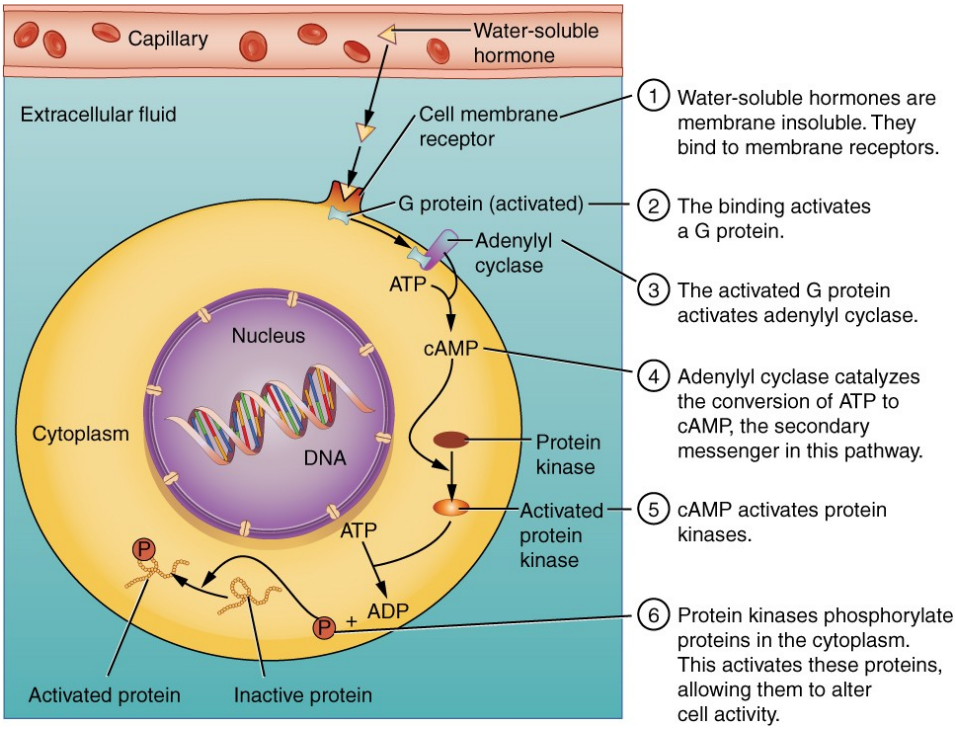


Figure 10.5: Binding of water-soluble hormones, from Openstax College[14]

In summary, lipid hormones hitch a ride through the blood and then enter the cell to activate gene expression. Non-steroid hormones move freely through the blood, but pass the message by knocking at the cell's door and transmitting the message to a second messenger which is already inside.

13 Cyclic adenosine monophosphate, which we met in the discussion of the lac operon regulation.

14 http://cnx.org/contents/FPtK1zmh@8.24:CTrkWxyU@3/Hormones.

The following table gives some information about the principal hormones.[15] We will then consider some examples.

Table 1: Some hormones of the endocrine system

Source	Hormones	Class	Effect
Pituitary (anterior)	Growth hormone (GH)	Protein	Growth of tissues
Pituitary (anterior)	Prolactin (PRL)	Peptide	Milk production
Pituitary (anterior)	Thyroid-stimulating hormone (TSH)	Glycoprotein	Thyroid hormone release
Pituitary (anterior)	Adrenocorticotropic hormone (ACTH)	Peptide	Adrenal cortex hormone release
Pituitary (anterior)	Follicle-stimulating hormone (FSH)	Glycoprotein	Gamete production
Pituitary (anterior)	Luteinizing hormone (LH)	Glycoprotein	Androgen production by gonads
Pituitary (posterior)	Antidiuretic hormone (ADH)	Peptide	Water reabsorption by kidneys
Pituitary (posterior)	Oxytocin (OT)	Peptide	Uterine contraction, lactation
Thyroid	Thyroxine (T_4), triiodothyronine (T_3)	Amine	Basal metabolic rate
Thyroid	Calcitonin	Peptide	Reduce blood Ca^{2+} levels
Parathyroid	Parathyroid hormone (PTH)	Peptide	Increase blood Ca^{2+} levels
Adrenal (cortex)	Aldosterone	Steroid	Increase blood Na^{+} levels
Adrenal (cortex)	Cortisol, corticosterone, cortisone	Steroid	Increase blood glucose levels
Adrenal (medulla)	Epinephrine, norepinephrine	Amine	Fight-or-flight response
Pineal	Melatonin	Amine	Regulate circadian rhythm
Pancreas	Insulin	Protein	Reduce blood glucose levels
Pancreas	Glucagon	Protein	Increase blood glucose levels
Testes	Testoserone	Steroid	Development of male secondary sex characteristics, sperm
Ovaries	Estrogens and progesterone	Steroid	Development of female secondary sex characteristics, preparation for childbirth

Now let's break it down some and take a look at components of the endocrine system.

15 Table after Openstax College,http://cnx.org/contents/FPtK1zmh@8.24:4lDC0JfF@3/An-Overview-of-the-Endocrine-S, with some modifications.

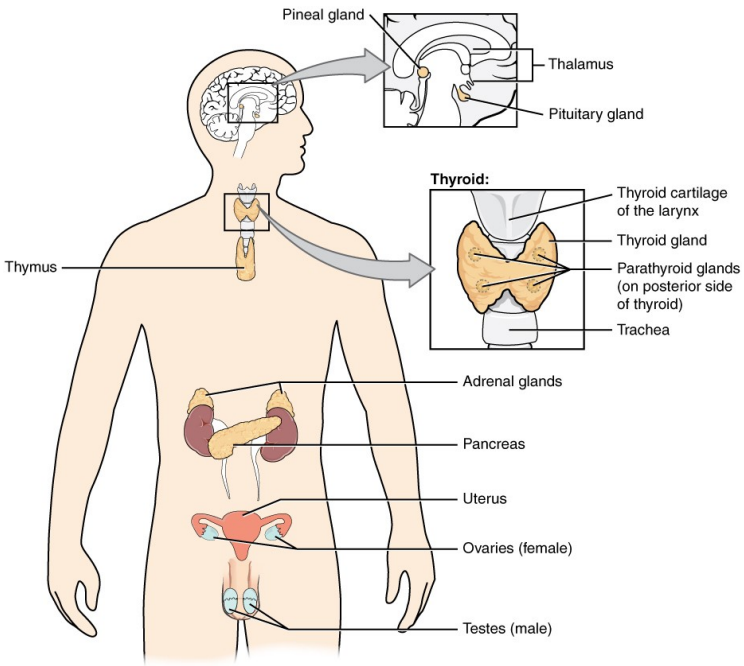


Figure 10.6: Endocrine glands and cells, from Openstax College[16]

10.3.1. The hypothalamus and the pituitary gland

The ***hypothalamus-pituitary complex*** is indeed complex. The hypothalamus, part of the diencephalon in the brain, as explained in paragraph 12.6.2, receives signals from many parts of the nervous system. It is the control center in which information from the nervous system is converted into requests for release or inhibition of release of hormones which then influence the body's metabolic activities. It does this by communicating through the pituitary gland, which is just below it in the brain. In brief, the nervous system controls the endocrine system by communicating with it through this interface, the hypothalamus-pituitary complex.

The pituitary gland consists of two lobes with rather different modes of functioning.

The ***posterior pituitary*** is really an outgrowth of the hypothalamus and is composed of nerve tissue. It stores two peptide hormones produced by the hypothalamus until the latter sends a nerve signal telling it to secrete some. Its two hormones are ***oxytocin*** (***OT***) and ***antidiuretic hormone***, or ***ADH*** (also called ***vasopressin***).

(It seems like it would be easier to refer to the posterior pituitary as the lower hypothalamus instead of a gland. That it is not may be for historical reasons.)

Oxytocin is important in women during childbirth, as cervical stretching increases oxytocin production to stimulate uterine contraction, and after, as receptors sensitive to suckling provoke oxytocin release to bring about contraction of milk ducts and ejection of maternal milk. In men and woman, it is related to parental-child bonding.

ADH is secreted when osmoreceptors in the hypothalamus detect abnormal concentrations of solutes in the blood. It signals the kidneys to absorb more water and send it into the blood stream to lower the concentration of such solutes.

Both oxytocin and vasopressin serve as neurotransmitters in the brain and may influence social interaction and bonding – and the opposite, depending on whether the social target is a member of the source's group.

16 http://cnx.org/contents/FPtK1zmh@8.24:4lDC0JfF@3/An-Overview-of-the-Endocrine-S.

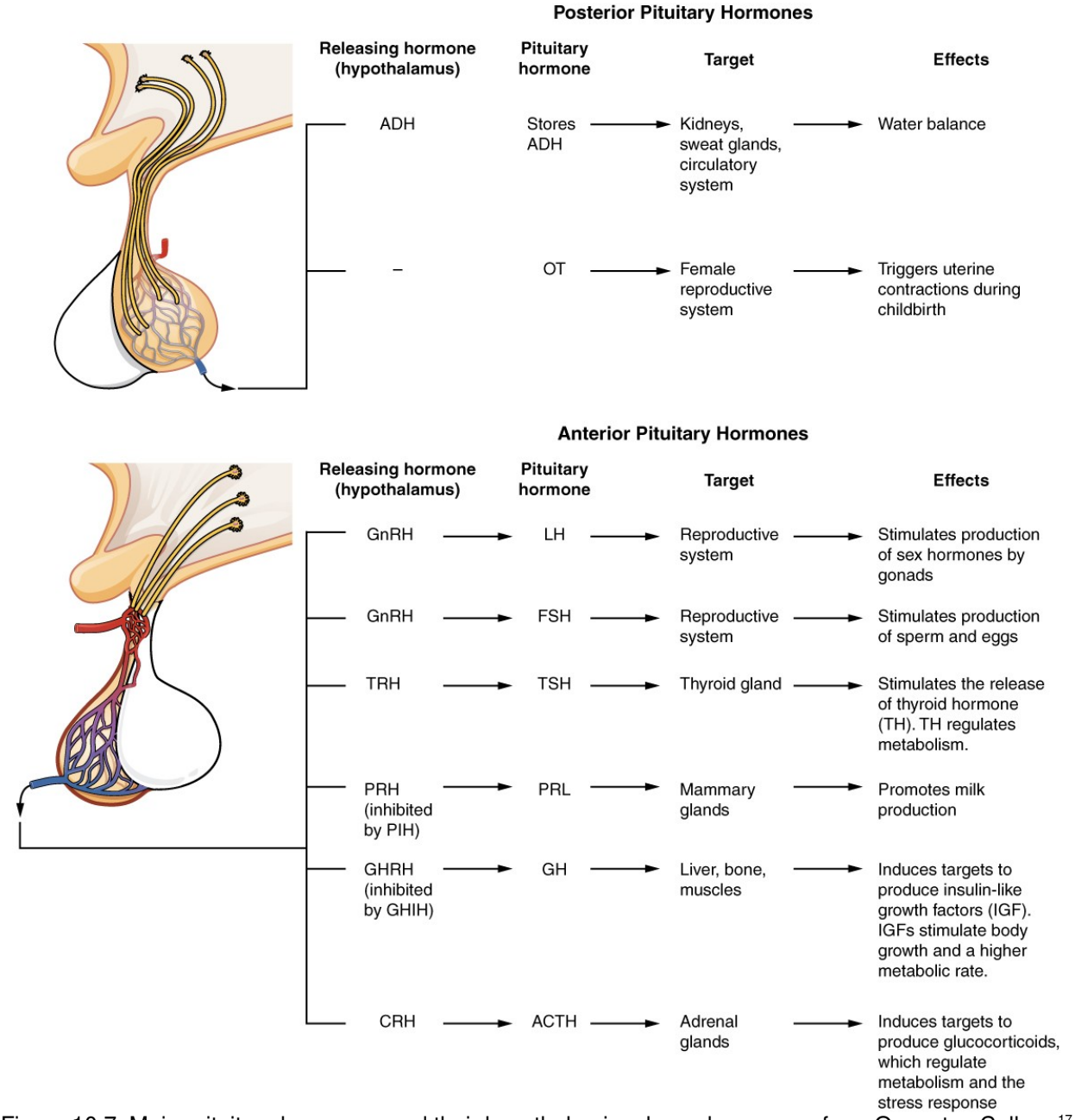


Figure 10.7: Major pituitary hormones and their hypothalamic release hormones, from Openstax College[17]

The ***anterior pituitary*** is composed of glandular tissue and synthesizes six principal peptide hormones. Although it makes its own hormones, it too is under the command of the hypothalamus, which communicates with it by a specific set of capillaries, the ***hypophyseal portal system***. The hypothalamus secretes four ***releasing hormones*** and two ***inhibiting hormones*** which control secretion by the anterior pituitary. The anterior pituitary, in turn, may secrete any of six hormones which stimulate other glands to release hormones to influence bodily functions. For instance, in response to TRH from the hypothalamus, the anterior pituitary secretes ***thyroid-stimulating hormone*** (***TSH***). TSH is a messenger which stimulates the thyroid gland to produce T_4 and T_3 hormones and these in turn control the rates of chemical reactions elsewhere. So control goes through several steps from the hypothalamus to the anterior pituitary and on to the thyroid which then tells some other organ to do its thing.

Of the six anterior pituitary hormones, four – called ***tropic hormones*** (trope = "turning") – regulate other endocrine glands: TSH, ACTH, FSH and LH .

17 http://cnx.org/contents/FPtK1zmh@8.24:IgqATiKA@3/The-Pituitary-Gland-and-Hypoth.

Why are the two parts of the pituitary considered to be one gland instead of two organs? Historical reasons? Be that as it may, the hypothalamus-pituitary pair can have direct effects, through hormones like OT or ADH, or indirect ones, by stimulating other glands to release hormones in a two-step control process. This explains why the pair has been referred to as the “command center” of the endocrine system.

10.3.2. The thyroid and parathyroid glands

As shown in Figure 10.8, the thyroid gland is located frontally at the base of the neck. Its follicles contain thyroglobulin, which contains tyrosine amino acids. Reception of TSH from the anterior pituitary gland causes active receptors on the follicle cells to transport I^- (iodide) ions into the cell, where they are oxidized to I_2. After peroxydase enzymes link them to tyrosine, the products finally form two hormones, ***triiodothyronine*** (***T_3***), containing three iodine atoms, or ***thyroxine*** (***T_4***), containing four.[18]

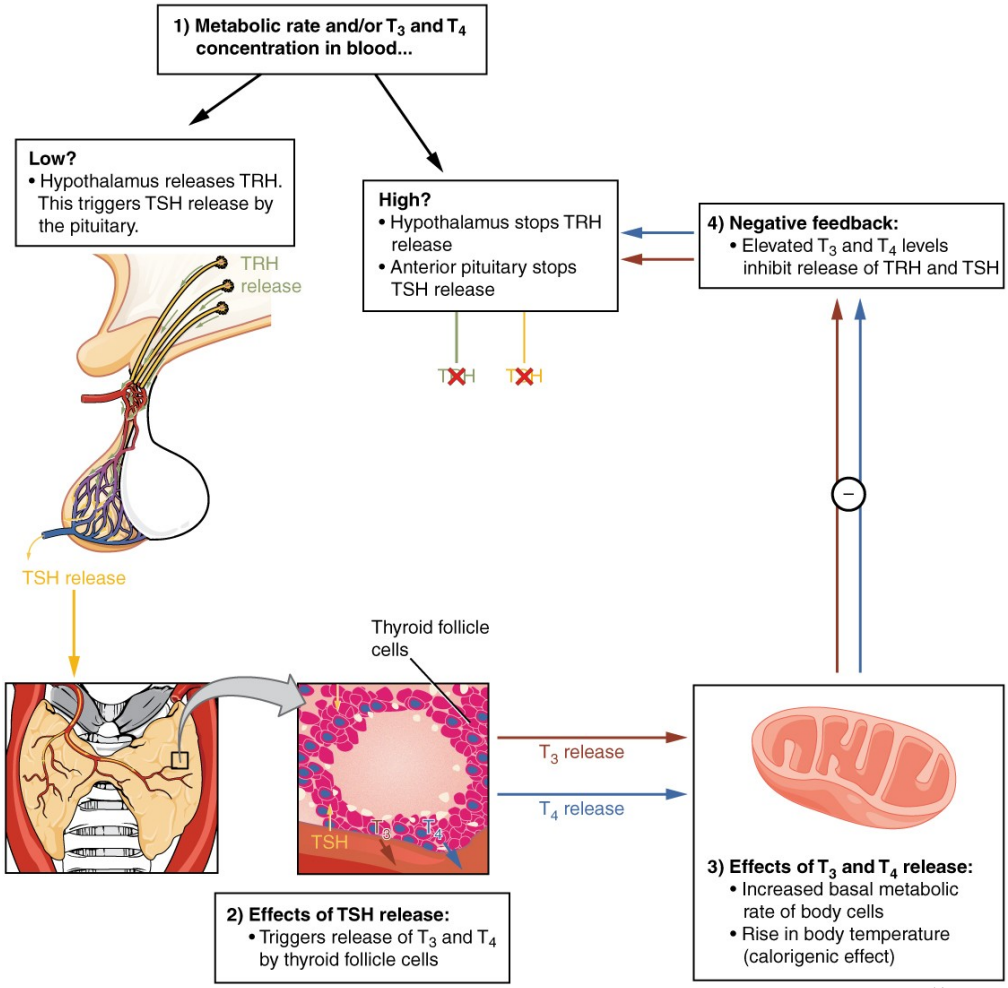


Figure 10.8: Regulation of thyroid hormone levels, from Openstax College[19]

If the hypothalamus detects low levels of T_3 and T_4 in the blood, it releases TRH into the anterior pituitary gland, triggering it to release more TSH which in turn signals the thyroid gland to release its hormones into the blood stream. The same system allows the hypothalamus to inhibit TRH release,

18 The explanation of this process given here is greatly simplified.

19 http://cnx.org/contents/FPtK1zmh@8.24:YhivaL0u@4/The-Thyroid-Gland

thus leading the thyroid to reduce emission of its hormones. This feedback mechanism is shown in Figure 10.8.

Thyroid hormones are extremely important, having an effect on almost every physiological process in the body. They influence the body's rate of ***basal metabolism***, the rate of energy use when at rest. They accomplish this by modifying the amount of respiration-related enzymes within mitochondria and by stimulating glycogen breakdown into glucose, the raw material for cellular respiration. Changing the metabolic rate also changes body temperature. Thyroid hormones also regulate rates of protein synthesis and so are important for growth, especially in young children. They even influence mental processes.

Thyroid hormones depend on an adequate level of iodine in the body. Too much (***hyperthyroidism***) or too little (***hypothyroidism***) can lead to symptoms such as reduced mental activity or mental retardation, goiters (swollen thyroid gland), fertility or development problems.

The thyroid also secretes ***calcitonin***, a hormone whose role is to bring about a reduction in Ca^{2+} levels in the blood. Its “other half” is ***PTH***. PTH is secreted by two to six tiny ***parathyroid glands*** on the posterior surface of the thyroid and stimulates an increase Ca^{2+} levels. This is accomplished largely by causing ***osteoclasts*** to break down old bone and release its calcium. The Ca^{2+} ion plays an essential role in the contraction of muscles and in the release of neurotransmitters in the brain, necessary for neurological functioning.

10.3.3. The adrenal glands

The adrenal glands sit on top of the kidneys (“ad” = near, “renal” = concerning the kidney). They are in two very different parts, the adrenal cortex and the adrenal medulla. The adrenal glands are important in the body's response to physical or psychological stress.

The ***adrenal cortex*** is the outer part of the gland and is composed of glandular tissue. It is stimulated when the hypothalamus emits the releasing hormone CRH, which tells the anterior pituitary to emit ACTH, which in turn signals the adrenal glands. The whole path is called the ***HPA*** (hypothalamus-pituitary-adrenal) axis. The adrenal cortex plays a role in long-term stress response. Three different parts of the cortex secrete different hormones.

- The outer cortex, the ***zona glomulerosa***, produces ***mineralocorticoids***, which control levels of electrolytes and liquids. The most important, ***aldosterone***, increases the amount of Na^{+} ions in the blood and the volume and pressure of the blood.
- The intermediate cortex, the ***zona fasciculata***, produces ***glucocorticoids***, which influence glucose metabolism. The principal one, ***cortisol***, plays a role in stress response by making body fuel more readily available through the conversion of glycogen to glucose, the breakdown of fatty acids and glycerol, and catabolism of muscles into amino acids. It also down-regulates the immune system, which explains its use against joint inflammation, such as in hydrocortisone creams. An excess of glucocorticoids is interpreted by the hypothalamus as a signal to stop emitting CRH, thus decreasing production of adrenal hormones – another example of control via feedback.
- The innermost cortex, the ***zona reticularis***, produces ***androgens***, such as testoserone.

The ***adrenal medulla***, in the inner part of the gland, is composed of neuroendocrine tissue and can be considered an extension of the autonomic nervous system. It is stimulated by the hypothalamus via neurons in the thoracic spinal cord, the sympathomedullary (***SAM***) pathway. Its major role is in short-term stress, which causes the sympathetic nervous system to alert the adrenal medulla to produce ***catecholamines***, the hormones ***epinephrine*** (perhaps better known as adrenaline) and ***norepinephrine*** (noradrenaline). These prepare the “***fight-or-flight***” response by converting glycogen into glucose, raising the level of blood sugar; raising the heart rate, pulse and blood pressure;

diverting blood away from digestion and other less immediate functions in order to increase the availability of oxygen; and partially down-regulating the immune system. Thyroid hormones can up-regulate catecholamine receptors in blood vessels.

Stress response may be divided into three phases called the ***general adaptation syndrome***, or ***GAS***:

1. The first stage is the ***alarm reaction***, the short-term "fight or flight" response initiated by the adrenal cortex's release of epinephrine or norepinephrine via the SAM pathway.
2. If the stress continues, the ***stage of resistance***, or adaptation, is entered. The body tries to adapt, for instance, by reducing physical activity.
3. If the stress lasts still longer, the ***stage of exhaustion*** arrives as the adrenal cortex releases hormones via the HPA axis, as described above. Results may be depression, immune system suppression or extreme fatigue.

10.3.4. The pineal gland

The function of the pineal gland, a tiny gland situated inferior and slightly posterior to the thalamus, is not entirely understood. Light impinging on the retina of the eyes travels up the optic nerve to the ***suprachiasmatic nucleus*** (***SCN***) of the hypothalamus, which passes a signal through the spinal cord and on to the pineal gland where it inhibits the production of ***melatonin***. This promotes wakefulness. The pineal gland therefore may influence the body's circadian rhythms. Melatonin is used by some air travelers in an attempt to diminish the effects of changes of time-zone.

10.3.5. Gonadol (sexual) and placental hormones

The gonads -- the male testes and female ovaries -- also produce hormones.

The principal hormone produces by the testes is ***testosterone***, affecting the male reproductive system and secondary sexual characteristics. A small amount of testoserone is also produced in ovaries.

The ovaries produce ***estrogens***, governing the female reproductive cycle, menstrual periods and female secondary sexual characteristics, and ***progesterone***.

During development, the female placenta produces both estrogens and progesterone, but also human chorionic gonadotropin (***hCG***) which reduces the immune system so that it will not reject the infant.

10.3.6. The pancreas

The pancreas is an organ with a double function. It contains ***exocrine*** cells, which release digestive enzymes directly into the small intestine. Such enzymes are essential for digestion, as we have seen in the chapter on that subject.

The pancreas also contains small structures call ***pancreatic islets*** which secrete hormones into the blood, The islets contain four types of cells.

- ***alpha cells*** produce ***glucagon***, which acts to raise blood glucose levels;
- ***beta cells*** produce ***insulin***, which causes lowering of blood glucose levels;
- ***delta cells*** secrete ***somatostatin***, which prevents simultaneous production of glucagon and insulin;
- ***PP cells*** produce ***pancreatic polypeptide hormone*** which plays a role in appetite and feelings of satiety.

We have already seen how glucagon and insulin effect changes in glucose levels in the blood by

modulating glucose uptake (absorption) and subsequent energy production by the cells (cellular respiration), the storage of glycogen in the liver (***glycogenolysis***), and the conversion of amino acids and glycerol into glucose (***glyconeogenesis***).

10.3.7. Endocrine functions of other organs

Other organs with endocrine functions are indicated in Table 1. In addition, there are a number of organs with other primary functions, but which also secrete hormones, including the heart and the skeleton. The following table covers these organs.

Table 2: Major hormones of organs with secondary endocrine functions, after Openstax College[20]

Organ	Major hormones	Effects
Heart	Atrial natriuretic peptide (ANP)	Reduce blood volume, pressure and Na^+ concentration
Gastrointestinal tract	Gastrin, secretin, cholecystokinin (CCK)	Aid digestion, buffer stomach acids
Gastrointestinal tract	Glucose-dependent insulinotropic peptide (GIP), glucagon-like peptide 1 (GLP-1)	Stimulate pancreatic beta cells to release insulin
Kidneys	Renin	Stimulate aldosterone release
Kidneys	Calcitriol	Aid absorption of Ca^{2+}
Kidneys	Erythropoietin	Trigger red blood-cell formation in bone marrow
Skeleton	Fibroblast growth factor 23 (FGF23)	Inhibit calcitriol production, increase phosphate excretion
Skeleton	Osteocalcin	Increase insulin production
Adipose tissue	Leptin	Promote satiety signals
Adipose tissue	Adiponectin	Reduce insulin resistance
Skin	Cholecalciferol	Modified to form vitamin D
Thymus (+ other organs)	Thymosins	Aid in T-lymphocyte production, more...
Liver	Insulin-like growth factor-1	Stimulate bodily growth
Liver	Angiotensinogen	Raise blood pressure
Liver	Thrombopoetin	Cause increase in platelets
Liver	Hepcidin	Blocks iron release into bodily fluids

We will encounter one of these organs in our study of the immune system – the ***thymus***. This small lymphoid organ is found between the heart and the sternum. It is important as the environment in which T cells mature after migration from the bone marrow where they are produced from

20 http://cnx.org/contents/FPtK1zmh@8.24:9VJJ4BqX@3/Organs-with-Secondary-Endocrin

hematopoietic stem cells.

10.3.8. A day in our endocrine system – hormones at work

A fun round-up suggested by a magazine article[21], shows the daily functioning of the endocrine system.

7:00. Before we wake up, cortisol secreted by the adrenal cortex reaches its maximum concentration, working to make energy and necessary substances available by increasing blood glucose levels. Under its influence, the liver produces more glucose, and the muscles and adipose tissue stock less of it. It also tells them to release amino acids from their stock of proteins and fatty acids from stored lipids.

8:00. The first peak of ghrelin, the "hunger hormones", produced by enteroendocrine cells of the gastrointestinal tract, especially the stomach. It acts on the brain to stimulate the appetite for breakfast. It will peak again around 13:00 and 18:00, with similar effects.

10:00. We need energy to get through the day's activities. Adiponectin is secreted primarily by adipose tissue, but also the muscles and even in the brain. It regulates glucose levels and fatty acid breakdown. It stimujlates muscles to use glucose rather than stock it and diminishes its production by the liver. It's an important anti-diabetic agent.

13:00. Dinner time, says ghrelin again.

14:00. Digestion increases the amount of glucose in the blood, bringing about more production of insulin by the pancreas telling the liver, muscles and adipose tissue to lower glucose concentration by storing it. If there is saturation of glucose storage, insulin tells the liver to convert more of it into glycogen. Liver production of sugars is inhibited so as to avoid hyperglycemia.

18:00. Again, ghrelin signals the imminence of supper.

20:00. With the onset of darkness, the pineal gland secretes melatonin which acts on our circadian cycle. It's released around 18-19:00 in winter, but only towards 21-22:00 in summer. It is one of those things which occurs less in older people, who tend not to sleep so well as when they were babies.

00:00. Leptin, secreted by adipose tissue when it is well stocked with fats, signals satiety, telling appetite centers in the hypothalamus that we shouldn't be hungry any more. Vasopressin, an antidiuretic hormone, tells the kidneys to slow down production of urine during the night. This not only limits night-time visits to the toilet, but avoids dehydration. Also, the pituitary gland emits growth hormone which profits from sleep to synthesize proteins in the muscles and use of fatty acids in adipose tissue.

10.4. The human circulatory system

We will consider the circulatory system only from a relatively high-level (undetailed) view of its structure and function – as a kind of plumbing system. This consists of several parts – the pump (the heart), the pipes (the veins and arteries) and the fluid (the blood).

10.4.1. The heart as pump – circulation

The heart consists of four chambers, two smaller, upper chambers – the ***atria*** (singular ***atrium***) – and two larger, lower ones – the ***ventricles***.

Even though we already indicated in the chapter on bioenergetics the general flow of blood through the heart and the cardiovascular circulatory system. it is worth repeating.

21 After "24 heures au rythme de nos hormones". Que choisir cahier santé no. 2 lié au numéro 188, December 2023.

Oxygen-depleted blood from the body enters the ***right atrium*** of the heart and is pumped into the ***right ventricle*** and thence through the pulmonary artery into the lungs. After picking up oxygen in the arterioles of the lungs, the blood returns through the pulmonary veins into the ***left atrium*** of the heart. It then is pumped into the ***left ventricle*** and out into the body via the aorta and arteries. In capillaries, oxygen passes into cells and the oxygen-depleted blood is then returned to the right atrium through veins and either the superior or inferior ***vena cava***.[22] Four valves – the ***mitral***, ***tricuspid***, ***pulmonary*** and ***aortic*** – keep the blood from flowing back in the wrong direction.

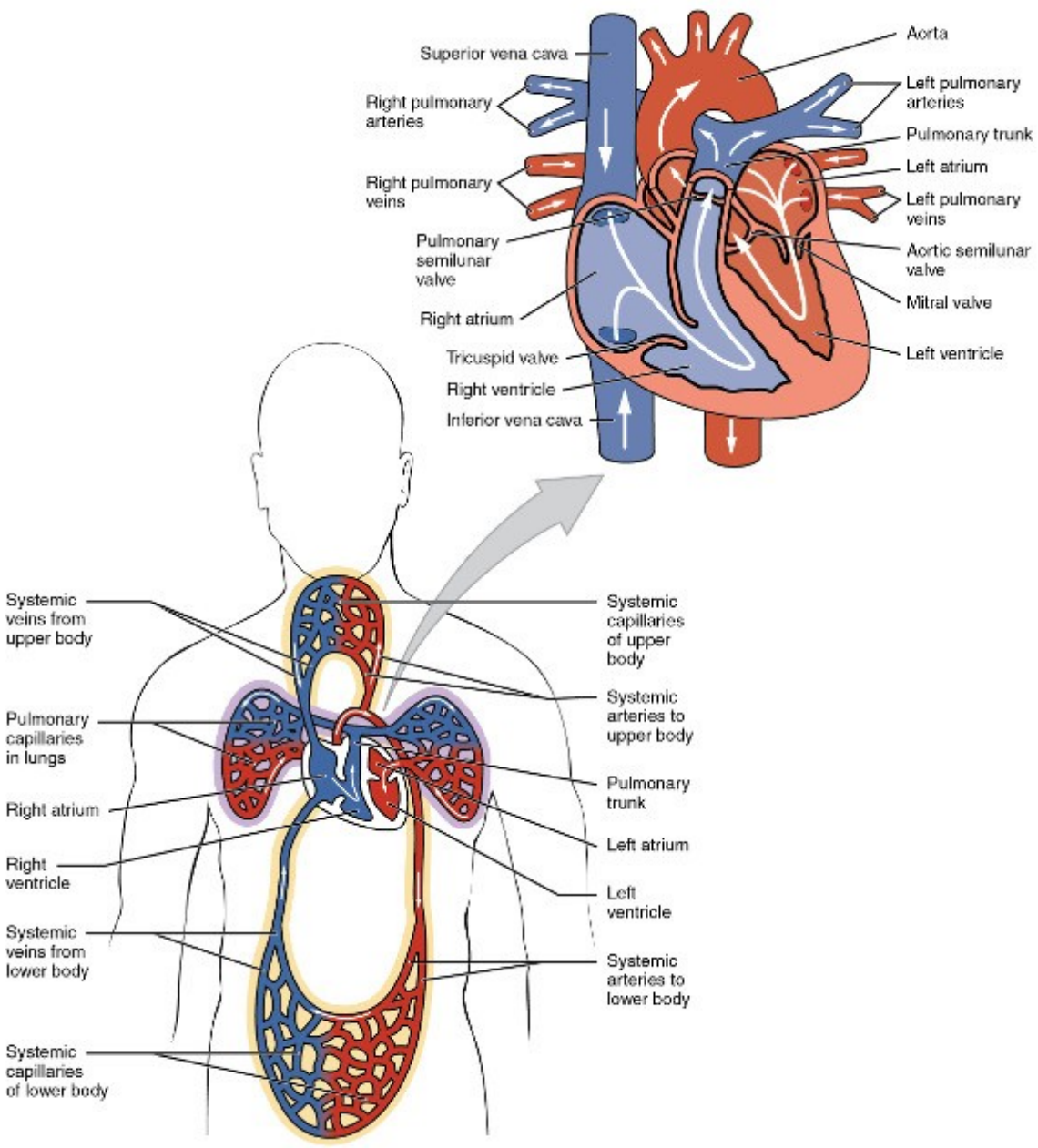


Figure 10.9: Cardiovascular circulation, from Openstax College[23]

The walls of the heart are composed of three layers of tissue: the ***epicardium*** (outer layer), the ***endocardium*** (inner layer) and, between them, the ***myocardium***, which is the thickest layer. The myocardium is the muscle which contracts to squeeze the four chambers and force blood from the

22 Remember, veins flow *towards* the heart, whether they contain oxygenated blood or not.

23 https://cnx.org/contents/FPtK1zmh@15.5:Y5T_wVSC@8/19-1-Heart-Anatomy

heart and out into the lungs or body. Being mostly muscle, the heart itself requires a considerable amount of energy and nutrients and, so, blood. This is supplied by the ***coronary arteries*** branching off the ***aorta***, the main exit for oxygenated blood. The heart pumps blood to itself.

In order to view up the entire circulatory system, one must also take into consideration the lymphatic system, which will be discussed in later paragraphs.

10.4.2. Electricity in the heart

Where study of the heart becomes really interesting is its electrical operation, where we meet our old friends energy and communications again.

The big question is, “What makes the heart beat?” Surprise: The commands to make it do so do not come from the brain. The brain can only modulate the rate of heartbeat.

The generation of an electrical signal to make the heart beat, i.e., to cause its muscles to contract in a rhythmic and well-synchronized manner, takes place in the ***sinoatrial*** (***SA***) ***node*** (or ***SAN***, or sinus node, or “pacemaker”) in the wall of the right atrium near the entrance of the superior vena cava. (See Figure 10.10.) Although similar signals may be generated elsewhere in the heart, they are usually overwhelmed by the higher-frequency SA signal. Like most cells in the body, the cell membranes of heart muscle contain a number of structures for allowing – or requiring – substances to enter or leave the cell. (We considered this in the biochemistry chapter.) Among these are Na/K pumps which maintain a negative voltage inside cell walls. In the SA node, however, instead of the usual voltage of around -80 Mv, slow leakage limits the voltage to -55-60 mV.

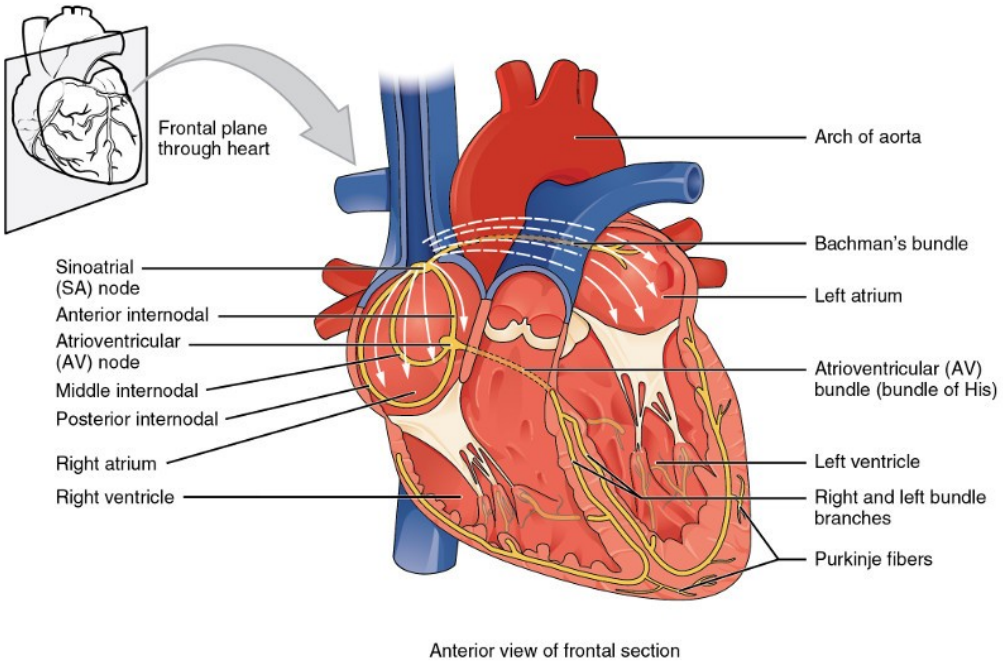


Figure 10.10: Conduction system of the heart, from Openstax College[24]

Startling fact: Embryonic heart cells kept alive in a Petri dish can generate an electrical impulse and contract. This is because heart cells undergo spontaneous depolarization to produce contraction.

Generation of an action potential in cardiac conductive cells takes place in four steps.

24 http://cnx.org/contents/FPtK1zmh@8.24:MCgS6S0t@3/Cardiac-Muscle-and-Electrical-

(1) The depolarization is due to “leakage” ion channels which allow some Na^+ to slowly enter the cell, gradually raising the SAN membrane potential from its minimum about -60 mV to -40 mV (the “prepotential” in Figure 9.8).

(2) This is the threshold value for a gated Ca-ion channel to open, allowing depolarization of the cell as Ca^{2+} ions enter.

(3) After about 100-150 milliseconds, the Ca^{2+} channels close and K^+ channels open. As K^+ rushes out of the cell, the potential re-descends to a bit under its initial resting value.

(4) Then the K^+ channels also close and the cycle starts over.

The result is a series of action potentials which cause the heart to beat all by itself.

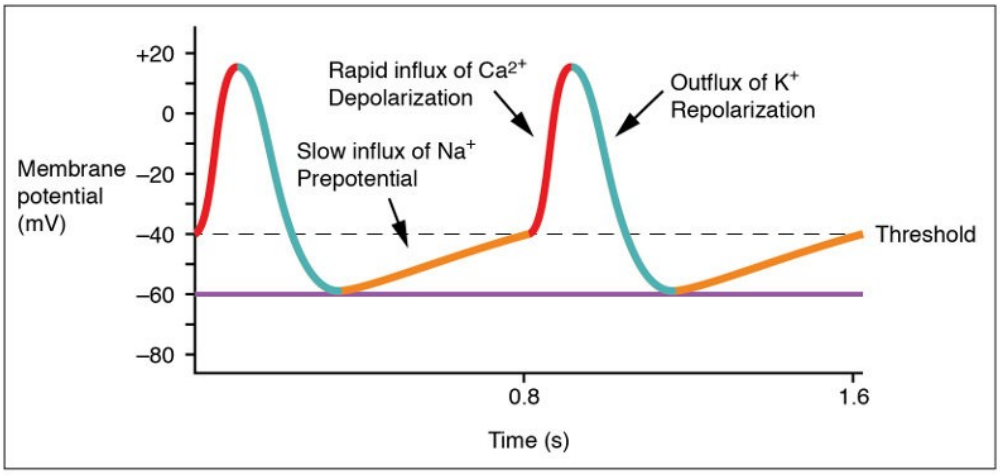


Figure 10.11: Action potential at the SA node, from Openstax College[25]

Not all heart cells are electrically conducting, so there are what amount to circuits which the generated electric signal can follow, as shown in the figure. The action potential generated in the SAN passes into atrial muscle fibers which contract and squeeze the atria. After traveling through the atria, the AP reaches the ***atrioventricular (AV) node***, where the "current" pauses for about 100 ms to allow the atrial contraction to terminate. The signal then continues from the AV node through the ***atrioventricular bundle*** (***bundle of His***) which separates into two different paths, the right and left ***bundle branches***, which control the right and left ventricles, respectively. Finally, the signal passes through ***Purkinje fibers*** which spread out through the ventricular myocardium, supplying current to bring about contraction to empty the ventricles.

So far, we have only talked about the form of an action potential in the conducting cells. When it reaches the contracting cells, which actually make the muscles squeeze the blood along its way, the form of the action potential is different.

25 https://cnx.org/contents/FPtK1zmh@8.119:MCgS6S0t@4/Cardiac-Muscle-and-Electrical-

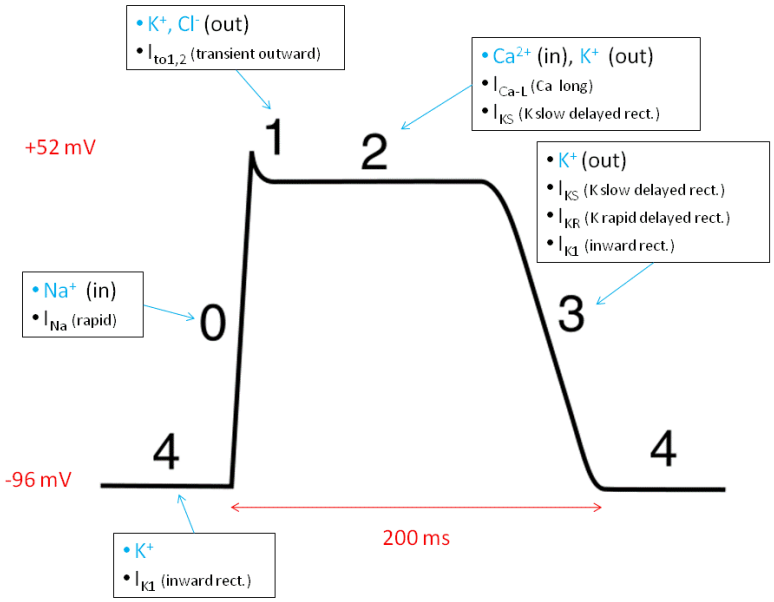


Figure 10.12: Ventricular action potential, by "Sylvia3" via Wikimedia Commons[26]

The ventricular contracting action potential in muscle tissue is shown in Figure 10.12. Resting ventricular potential is around -90 mV, but opening of fast Na+ channels initiate a fast depolarization. Then the fast channel closes but relatively slow Ca^{2+} channels open, allowing Ca^{2+} to enter, maintaining the potential at a plateau until the Ca^{2+} channels close at around 0 mv and the K^{+} channels open again and repolarize the cell. This long plateau, or refractory period, of about 200 ms allows time for blood to flow and avoids premature contractions which would disrupt the synchronization of the contractions.

10.5. The cardiac cycle

A trace of the heart's electrical signals can be detected on the surface of the skin by an electro-cardiogram (ECG or sometimes EKG) and show the patterns of atrial and ventricular ***systole*** (contraction to pump blood out of the heart) and ***diastole*** (relaxation while the chambers refill with blood). The output shows cycles of the heart's functioning over several steps, called the ***cardiac cycle***. It goes like this:

1. All chambers are relaxed (diastole) and blood flows into them, filling them to about 70-80% of their capacity. Valves keep blood from flowing in the wrong direction.
2. Depolarization in the SA node starts a series of action potentials which cause atrial contraction (systole) which forces the rest of the blood into the ventricles, filling them completely. This is shown as what is called the P wave on the ECG output. The signal moves down to the AV node, where there is a delay. After about 100ms,the atria relax and enter their diastole phase. They have now completed their activity for this cycle.

26 https://commons.wikimedia.org/wiki/File:Action_potential_ventr_myocyte.gif

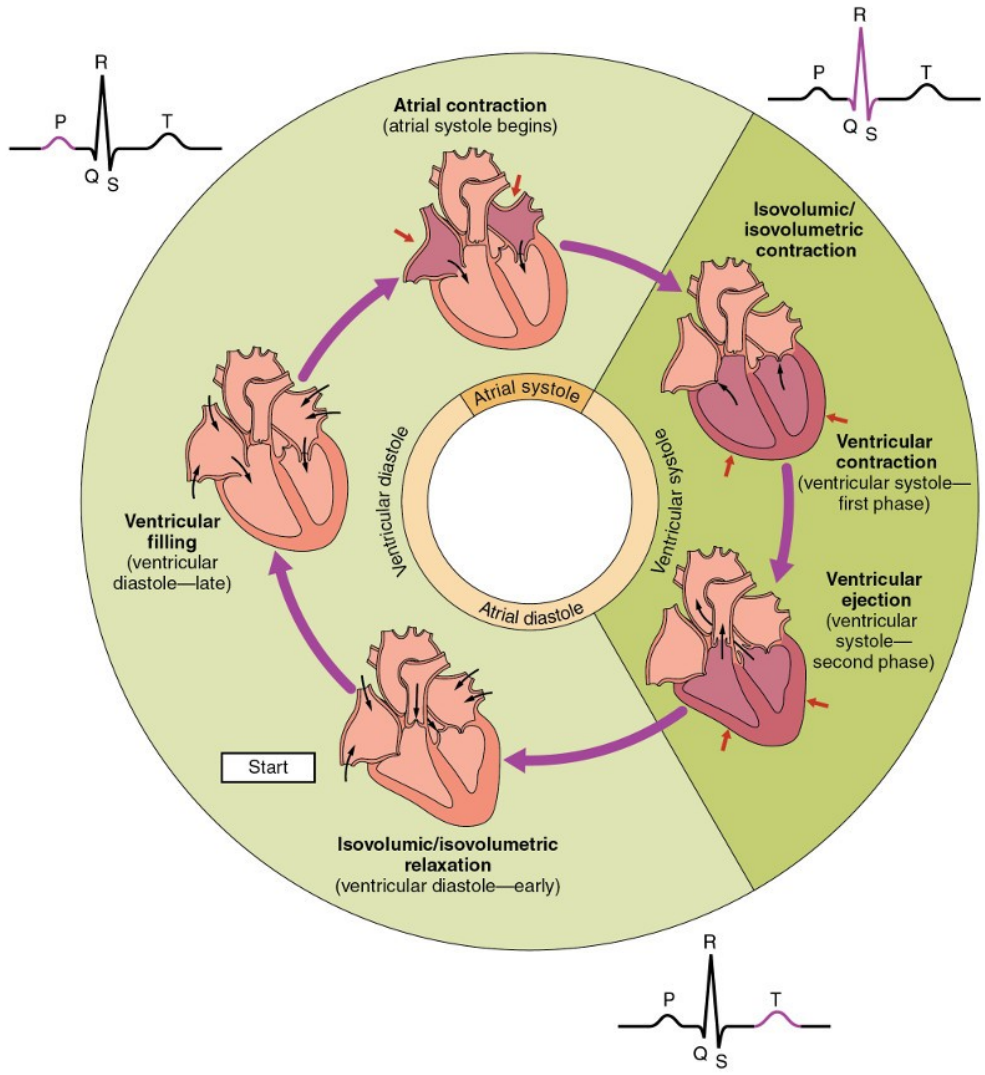


Figure 10.13: Phases of the cardiac cycle, from Openstax College[27]

3. The action potential moves down through the bundle branches and through the Purkinje fibers, launching ventrical systole. The signal reaches the right ventricle first, so it starts to contract slightly before the left. The increased pressure closes the tricuspid and mitral valves to the atria and opens the pulmonary and aortic exit valves (semilunar valves). Blood flows out to the lungs and the body. This stage shows up on the ECG as the QRS complex and lasts about 270ms. Blocks in the branches which impede the signal for whatever reason alter the form of the QRS signal.
4. The ventricles relax into diastole at the T wave. Ventrical diastole lasts about 430ms.

The cycle starts over – constantly, all the time we are alive, from our heart's formation during embryonic development to our last moment of life.

The “lub-dub” sound of a heartbeat, familiar to doctors with stethoscopes and to horror-movie fans, corresponds to the opening and closing of the semilunar (aortic and pulmonary) valves and so to the beginning and the end of the ventricular systole.

27 http://cnx.org/contents/FPtK1zmh@8.24:IsP5aaud@3/Cardiac-Cycle

10.5.1. Regulation of heart rate

Adding up the duration of the phases indicated above gives 100+270+430 = 800ms per heartbeat, or 75bpm (beats per minute), the average rate for an adult. Although the heart itself is responsible for its beating, both the heart contraction rate (***HR***) and the volume of the chambers (***stroke volume***, ***SV***) are influenced in several ways.

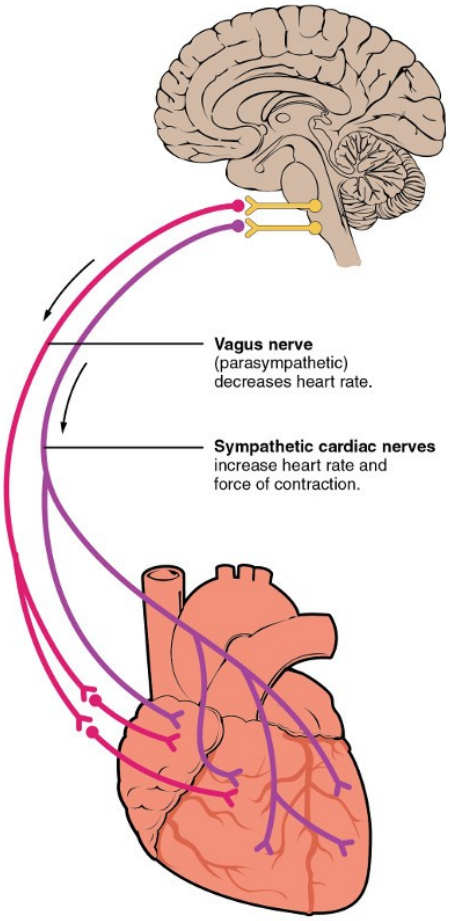


Figure 10.14: Autonomic innervation of the heart, from Openstax College[28]

Nervous system influence on the heart originates in ***cardiac centers*** of the medulla oblongata of the hindbrain, just in front of the cerebellum (Figure 10.14). Nerve fibers from this region reach several parts of the heart, including the SA and AV nodes and both atria and ventricles. The sympathetic nervous system (e.g., “fight or flight”) releases norepinephrine (NE) which speeds up the heart rate. The parasympathetic system sends acetylcholine (Ach) along the vagus nerve which slows the heart rate. At rest, both (but mostly the parasympathetic) contribute to ***autonomic tone***, which would otherwise be about 100bpm.

28 http://cnx.org/contents/FPtK1zmh@8.24:STUWOAmw@5/Cardiac-Physiology

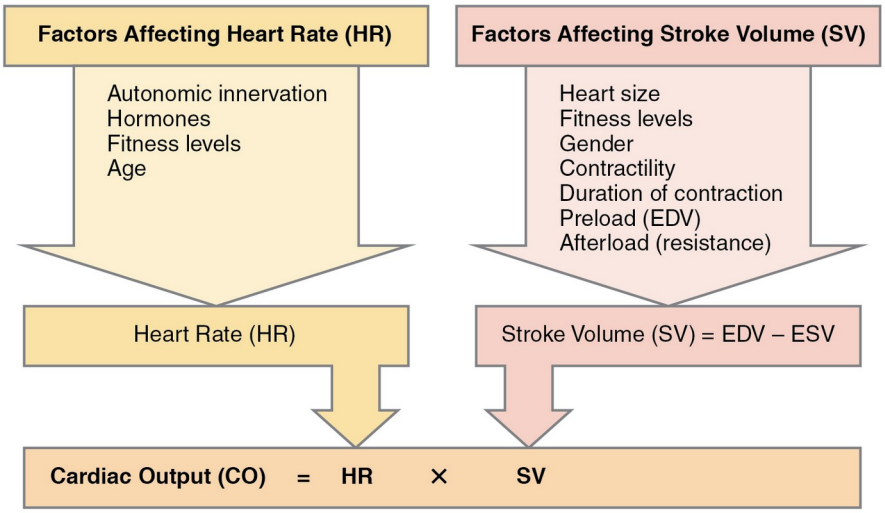


Figure 10.15: Major factors influencing cardiac output, from Openstax College[29]

Increased physical activity detected by proprioreceptors, changes in blood pressure or flow detected by barioreceptors (stretch) or metabolic activity detected by chemoreceptors send data to the cardiac centers which then regulate heart beat and flow appropriately. Hormones, ion concentrations, temperature, pH and stress (via the limbic system) all have an influence.

Bear in mind that the heart is a muscle and, like the other muscles, needs regular exercise.

10.5.2. The blood

The production of blood and lymphatic system cells from hematopoietic stem cells is shown in Figure 10.19. However, the blood contains other components, listed in Figure 10.16.

Biologists distinguish four types of tissue:

1. ***epithelial tissu***e (***epithelium***) covers surfaces, inside the body and out;
2. ***muscle tissue*** contracts and consists of three types: skeletal (voluntary), smooth and cardiac;
3. ***nervous tissue*** propagates electrochemical signals.
4. ***connective tissue*** provides binding, support, protection and integration;[30]

Blood is considered to be connective tissue.[31] Connective tissue consists of cells which are relatively far apart, compared to epithelial cells, and which are dispersed within a ***matrix***, usually a liquid. The cells of blood, called the ***formed elements***, float in an extracellular matrix called ***plasma***, which is mostly water. The components of blood are shown in the following table.

Although blood plasma is about 92% water, it does contain three types of plasma proteins as well as small amounts of other substances.

Aside from water, the major components of the plasma are albumin and and globulins. ***Albumin*** binds to lipids and transports them through the hydrophilic plasma. It also serves to regulate osmotic pressure. ***Globulins***, or gamma globulins, are ***immunoglobulins***, i.e., antibodies, about which more shortly.

Blood serves many purposes, but the most important (although it could not go on without the others) is the transport of oxygen, nutrients and waste matter, such as carbon dioxide.

29 http://cnx.org/contents/FPtK1zmh@8.24:STUWOAmw@5/Cardiac-Physiology

30 To my mind, connective tissue is “all the rest”.

31 Obviously, it is not one of the others.

The transport of oxygen is carried out by ***erythrocytes***, or red blood cells (RBC), which make up 99% of the formed elements. They are so numerous, they make up approximately 25% by number of all the cells in the body.

Component and % of blood	Subcomponent and % of component	Type and % (where appropriate)	Site of production	Major function(s)
Plasma 46–63 percent	Water 92 percent	Fluid	Absorbed by intestinal tract or produced by metabolism	Transport medium
	Plasma proteins 7 percent	Albumin 54–60 percent	Liver	Maintain osmotic concentration, transport lipid molecules
		Globulins 35–38 percent	Alpha globulins—liver	Transport, maintain osmotic concentration
			Beta globulins—liver	Transport, maintain osmotic concentration
			Gamma globulins (immunoglobulins)—plasma cells	Immune responses
		Fibrinogen 4–7 percent	Liver	Blood clotting in hemostasis
	Regulatory proteins <1 percent	Hormones and enzymes	Various sources	Regulate various body functions
	Other solutes 1 percent	Nutrients, gases, and wastes	Absorbed by intestinal tract, exchanged in respiratory system, or produced by cells	Numerous and varied
Formed elements 37–54 percent	Erythrocytes 99 percent	Erythrocytes	Red bone marrow	Transport gases, primarily oxygen and some carbon dioxide
	Leukocytes <1 percent Platelets <1 percent	Granular leukocytes: neutrophils eosinophils basophils	Red bone marrow	Nonspecific immunity
		Agranular leukocytes: lymphocytes monocytes	Lymphocytes: bone marrow and lymphatic tissue	Lymphocytes: specific immunity
			Monocytes: red bone marrow	Monocytes: nonspecific immunity
	Platelets <1 percent		Megakaryocytes: red bone marrow	Hemostasis

Figure 10.16: Major blood components, from Openstax College[32]

As an erythrocyte develops in the marrow of large bones, it ejects most of its organelles, including the nucleus and the mitochondria. Without mitochondria, it is only capable of anaerobic respiration, which prevents its using up the very oxygen it is transporting. Erythrocytes are shaped like tiny disks, thinner in the middle, which enables them to fold up to fit through small openings in capillary walls. They are extraordinarily well adapted to their function. For instance, the absence of many internal organelles leaves more space for the molecule which transports oxygen: hemoglobin.

32 http://cnx.org/contents/FPtK1zmh@8.24:IUrEdFyf@7/An-Overview-of-Blood

A molecule of ***hemoglobin*** is made up of four folded protein chains called ***globin***, each one of these attached to a red pigment molecule called ***heme***, which contains one ion of iron, Fe^{2+}. To each iron ion, one molecule of oxygen can bind for transport, making four oxygen molecules per hemoglobin molecule. The result is called ***oxyhemoglobin*** and constitutes the bright red blood which flows in non-pulmonary arteries and pulmonary veins. The oxygen-transporting capacities of the body's hemoglobin are quite phenomenal. One erythrocyte contains about 300 million hemoglobin molecules and so binds up to 1.2 billion oxygen molecules.

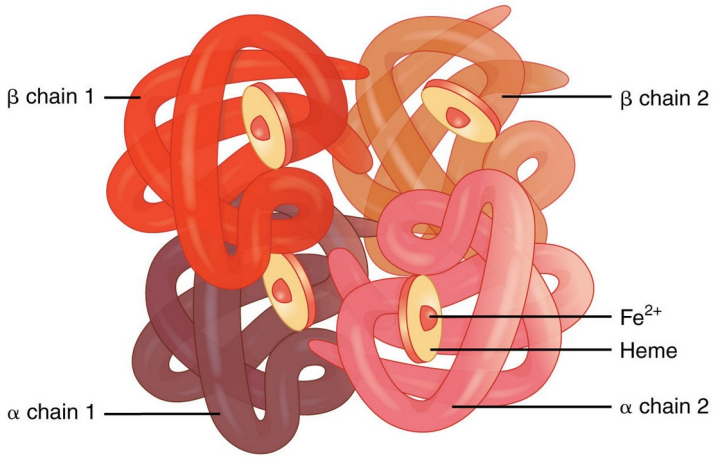


Figure 10.17: Hemoglobin molecule, modified after Openstax College[33]

Even so, there are not too many. If the number goes down, we suffer from anemia, if not something worse. The composition of hemoglobin underlines the necessity of small amounts of trace elements like iron in the body.

The amount of oxyhemoglobin is in equilibrium with the milieu:

- A higher concentration of oxygen leads to a greater amount of oxyhemoglobin formed;
- a lower concentration of oxygen causes oxyhemoglobin to dissociate into oxygen and hemoglobin.

This explains why oxyhemoglobin forms in the oxygen-rich lungs and dissociates in the capillaries where oxygen is less concentrated. In addition, the presence of CO_2 in the blood somewhat increases the dissociation of oxyhemoglobin.

10.6. The lymphatic system

The lymphatic system, constituted of the lymph vessels and nodes and the lymph, serves several functions.

A partial. parallel venous system

In the circulatory system, the heart pumps blood throughout the body via arteries, then smaller arterioles and finally through tiny capillaries, from which molecules are exchanged with cells and the rest of the body. Due to the pressure of the blood, much plasma is also released. The endothelial walls of the capillaries are just one cell thick and the spaces between them allow fluid to pass, but not the larger erythrocytes (RBCs), which therefore remain in the blood.

Outside the capillaries, the escaped fluid and molecules make up part of the ***extracellular*** or ***interstitial fluid***. It is composed of WBCs, including lymphocytes, some hormones, glucose and other molecules, such as proteins and lipids. Much of it is reabsorbed, but some remains outside. One of

33 http://cnx.org/contents/FPtK1zmh@8.24:9SrcxH7k@4/Erythrocytes

the jobs of the lymphatic system is to carry it back into the blood stream.

The lymphatic system therefore can be considered a parallel path to the venous system, but it carries no RBCs, only WBCs, called ***leukocytes***. The ***lymph***, as the fluid is called when it is inside the lymphatic system, is returned to the veins at two ducts placed strategically where blood pressure is relatively very low and the liquid can therefore be transferred into the vein easily.

Lymph is not pumped by the heart. Smooth muscles in the walls of the lymph vessels, as well as skeletal muscle, squeeze the lymphatic vessels, pushing the lymph through one-way valves which prevent its returning to the capillaries. Similar valves allow the interstitial fluid to enter the lymph vessels but not to leave them. Lymph flows from ***lymphatic capillaries***, or ***terminal lymphatics***, and into bigger lymph vessels before re-entering blood veins in either the ***right lymphatic duct*** (which drains the upper right-hand side of the body) or the ***thoracic duct*** (which drains all the rest).

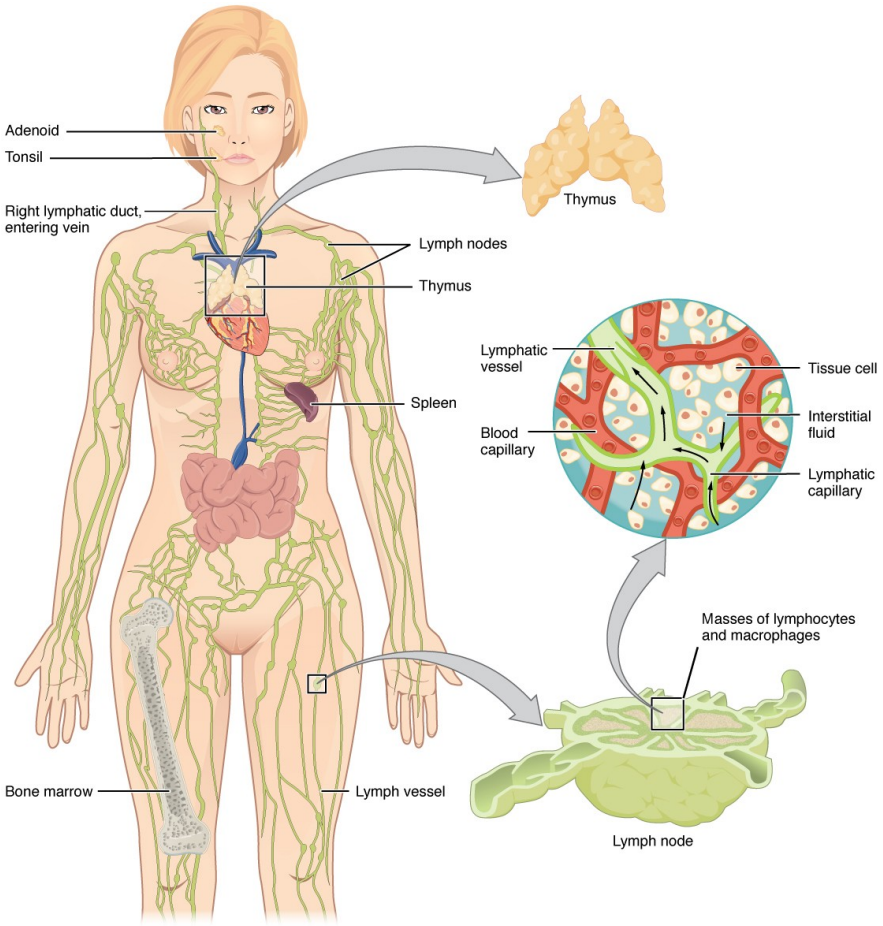


Figure 10.18: Lymphatic vessels, from Openstax College[34]

Immune system function

The lymphatic system is much more than a simple alternate return route for WBCs. Since it carries lymphocytes, it is crucial for the immune system. Scattered about the body along the lymphatic vessels are some 500-600 special tissues (too small to be called organs) called ***lymph nodes***, in which immune-system cells do much of their work.

There are macrophages present in all tissue, but most of the immune-system cells spend their off-duty hours in the lymph nodes. The complicated process of B-cell and T-cell growth and activation (to be discussed in the next section) is carried out more rapidly in an environment where macrophages or dendritic cells and B and T cells proliferate and this is in the lymph nodes. The large number of such

34 http://cnx.org/contents/FPtK1zmh@8.24:xEZkXdm8@5/Anatomy-of-the-Lymphatic-and-I

cells, as well as macrophages and others, means that the lymph passing through the node has most if not all its pathogens filtered out and phagocytized.[35]

The ***spleen*** is not connected to the lymphatic vessels, but It contains a large number of macrophages and dendritic cells which carry out a similar filtering process not on lymph, but on the blood.

Other secondary lymphoid tissues are:

- lymphoid nodules, such as the tonsils, in the respiratory and digestive tracts, which contain dense clusters of lymphocytes;
- mucosa-associated lymphoid tissue (MALT);
- bronchus-associated lymphoid tissue (BALT).

Function with other molecules

Glucose in the small intestine diffuses out of the intestine, into capillaries and thence throughout the the body via the circulatory system. But lipids leave the small intestine in the form of ***chylomicrons***, which are too large to enter capillaries. However, they can enter the lymphatic system ***lacteals***, lymphatic capillaries in the intestinal villi. The lymphatic system then conveys the lipid-bearing chylomicrons into the blood.

In a similar way, other molecules, such as some hormones, or waste products, being sent to the liver or kidneys, and which are produced not in the blood but elsewhere in the body, may not be able to enter blood capillaries, and so flow into the circulatory system via the lymphatic system.

10.7. The immune system

The immune system is complex, multi-leveled and multi-component.[36] Even though much has been learned about it in recent decades, it is still under intense investigation. One book says: "The immune system is a collection of barriers, cells, and soluble proteins that interact and communicate with each other in extraordinarily complex ways."[37] We agree. So, rather than starting out with lists of the components, the structures and so forth, let's look at an example.

10.7.1. Overview – physical barriers and inflammation

Suppose something bad – a virus or a mean bacteria – gets into a body. What happens then to protect against this pathogen?

The first line of defense against pathogens is largely mechanical or chemical. It comprises such things as the skin, which forms a natural ***barrier*** to keep things out; the ***mucus*** in our respiratory system, which captures microbes in the air we breathe and, by means of tiny hairs – ***cilia*** – drags them back up to where we can swallow them[38]; and the gastrointestinal system, which is highly acid and can therefore kill many invaders.

But some of the invaders get past these barriers. And some do not even need to, because they show up internally. Tissue damage can result from external sources also, as when a hammer is injudiciously applied to a thumb. So after the barrier layer, what then?

The next step is often inflammation, called the ***inflammatory response***. The infected area turns red,

35 These terms will be explained in the next section.

36 Its complexity and numerous components, which are not independent or separable for study, has led to confusion in the designation of its sub-systems. (Author's opinion.)

37 Openstax College, Anatomy and physiology (2013), 94.

38 Yuk.

swells up, becomes hot and hurts. This region is the battlefield where the fight carries on after the barriers have been breached – where the various cells of the immune system go about protecting us.

Injured cells call for help by releasing chemical messengers called ***chemokines*** into the interstitial fluid. These indicate to cells farther away that there is a problem to be solved and implores their assistance. The cavalry arrives not by following a trumpet call, but by moving against the gradient of the chemokines, toward their point of greatest concentration, in a process called ***chemotaxis***.[39]

Among those coming to help, ***mast cells*** are one of a group of cells which contain granules, from which they release histamine, leukotrienes and prostaglandins. These chemicals cause ***vasodilation***: Blood vessels expand so more blood can come in, bringing help, but they also become porous. Increased blood flow and plasma leakage into the interstitial space are responsible for the heat and redness and painful swelling.

Chemokines also lure in ***phagocytes***, special cells which surround and absorb pathogens. First to arrive are ***neutrophils***, the most plentiful phagocytes in the body. They are soon joined by other phagocytes – ***macrophages*** and ***dendritic cells*** – which come to phagocytize pathogens, to engulf them and destroy them in the process of ***phagocytosis***. All the cells mentioned so far are part of the non-specific or ***innate response***. They are non-specific because each of them may act against any pathogen. Because they all rush in, they operate quickly, but they are neither very precise nor very efficient.

Now we reach the next level of the immune system, the specific immune system, or ***adaptive immune response***, as ***B cells*** and ***T cells*** begin to do their thing.

The adaptive response distinguishes one pathogen from another and so can adapt to deliver a response specific to each one. Not only that, it has a memory and remembers the pathogens it has already met. This capability depends on identification of the pathogen by means of recognizable structures called ***antigens*** (from ***anti***body ***gen***erations), or ***antigenic determinants***, which are part of the surface of the pathogen. Phagocytes such as macrophages. dendritic cells or B cells, extract the antigens from the pathogen itself and display them on their own surface. This enables a specific response, one depending on the identity of the pathogen. Such a series of events takes more time than the innate response, but because it is adaptive and specific to the particular pathogen, it is usually more effective. The complicated procedure necessary to create adaptive-response cells guarantees to a high degree that the immune system will only react to pathogens and not to ordinary body cells, as happens in lupus, which could be fatal.

Macrophages which display antigens on their surface serve as messengers or links between the innate and adaptive responses and begin the intricate process by which B cells, with the collaboration of T cells, produce ***antibodies***, which protect us over time.

The ***complement system*** is composed of proteins which aid immune response. They may, for instance, bind to a pathogen and thus label it – ***opsonization*** – calling attention to it so that phagocytes will deal with it. The complement system can help out both the non-specific and specific responses.

Now let's look at these different immune-system components in more detail.

10.7.2. Innate immune response

The ***innate***, or non-specific, immune system depends on several types of cells. It most likely evolved before the adaptive immune response.

One group of cells is constituted of ***phagocytes***, which can engulf and contain pathogen cells, a process called ***phagocytosis***. The contained pathogen, called a ***phagosome***, is usually killed by a lysosome in the phagocyte cell. A phagocyte recognizes pathogens in a somewhat approximate way,

39 Neutrophil to driver: "Follow that chemokine!"

as its surface (not to mention its genes) can contain only a certain number of antigen ***pattern recognition receptors*** (***PRR***s). Phagocytes are also important because they represent the first step in the process which identifies pathogens and leads to the release of specific antibodies. There are several phagocytes associated with the innate immune response.

- A ***macrophage*** is an amoeba-like phagocyte which can squeeze through tissues and capillary walls. It is capable of phagocytizing quite large bacteria.
- A ***neutrophil*** is a spherical phagocyte summoned from the blood stream. It is a ***granulocyte***, meaning that it contains granules of substances such as histamine,. It is the most abundant of the white blood cells (***WBC***s).
- A ***dendritic cell*** is an irregularly shaped cell with many appendages looking like the dendrites on neurons, hence the name. However, they are not neurons. Although they may be partly phagocytotic, their principal function is as antigen-presenting cells, about which more very soon.
- A ***monocyte*** is a precursor cell which may mature into either a macrophage or a dendritic cell.

A ***natural killer cell*** (***NK***) is not generally considered a phagocyte, but it is capable of convincing a pathogen cell to commit suicide, or ***apoptosis***. It may do this through the use of a special ligand or by releasing ***perforin*** to bore a hole in the cell wall and then cause ***granzyme*** to enter the cell and bring about apoptosis.

10.7.3. Leukocytes (WBCs) and lymphocytes

Blood cells are all differentiated from ***hematopoietic stem cells***, or ***HSCs***, (Figure 10.19) in the marrow of bones. HSCs differentiate into two paths corresponding to each one's precursor stem cell, myeloid or lymphoid.

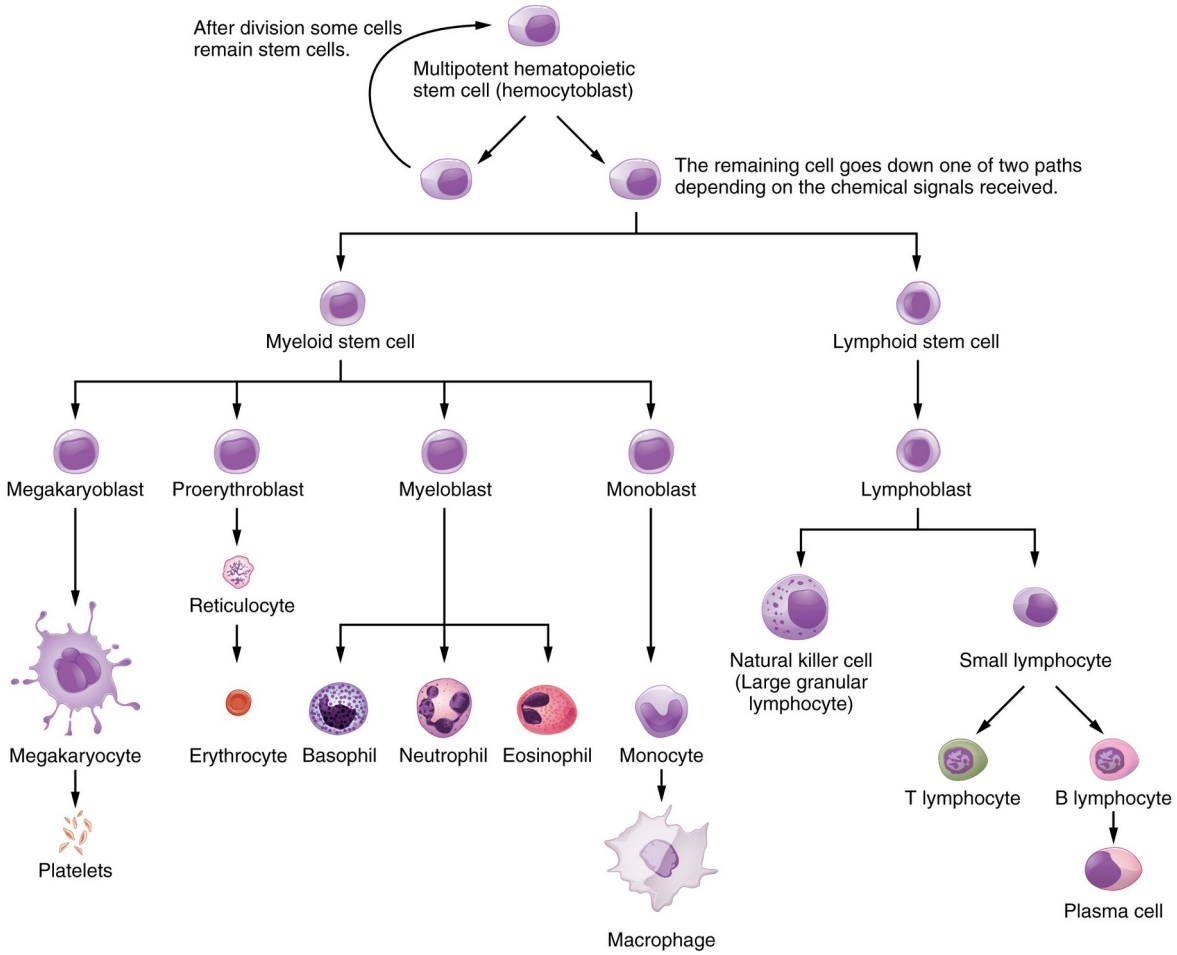


Figure 10.19: Differentiation of hematopoietic stem cells, from Openstax College[40]

Erythrocytes are red-blood cells, of which the adults contain no nuclei, and ***platelets*** are responsible for blood clotting (coagulation). The other myeloid cells shown are all WBCs, or ***leukocytes***. In the lymphatic system, they are called ***lymph***. They also constitute the interstitial fluid between cells.

NK cells, B cells and T cells are called ***lymphocytes***, as are plasma cells which develop from B cells. Whereas the NK and B cells mature in bone marrow, T cells migrate to the thymus for maturation, hence the T. After strong selection against cells which may attack their own organisms, both types of cells migrate to lymphoid tissue throughout the body. NK cells are part of the innate immune system. B and T cells are cells of the adaptive immune system.

Dendritic cells, not shown in the figure, are special, existing in several varieties, and can come from a myeloid or a lymphoid precursor.

Each instance of a B or T cell has surface receptors which can be activated by only one type of antigen. Therefore, in order to detect almost any pathogen, the great number of B-cell and T-cell receptors necessary would require more genes than exist in our DNA. This difficulty is overcome by means of an astounding technique – ***gene shuffling***. During the expression of their genes, segments of genes are shuffled like cards, giving over 10^{11} possible combinations, each of which detects a specific antigen.

B and T cells must be activated by presentation of their specific antigens in the manner we shall see next. NK cells do not require activation. When a lymphocyte is presented its specific antigen, it becomes activated and reproduces abundantly by mitosis. (B cells also require the help of special T cells, as we shall see in a moment.) Activated B cells produce antibodies. Groups of such cells

40 http://cnx.org/contents/FPtK1zmh@8.24:xEZkXdm8@5/Anatomy-of-the-Lymphatic-and-I

activated by and sensitive to a specific pathogen are called ***clones***[41], so cells of a clone share the same antigen receptors. Only lymphocytes which are activated by an antigen reproduce and multiply into clones, so the process can be seen from the viewpoint of natural selection: Only activated cells survive and reproduce.

10.7.4. Antigen-presenting cells (APCs)

The mechanisms of antigen presentation are somewhat complex. ***Antigen-presenting cells*** (***APCs***) internalize the pathogen or antigen, break it up and bind pieces of it with a protein called the ***major histocompatibility complex*** (***MHC***) molecule. T cells can only recognize the complex formed by both the MHC molecule and the antigen and presented on the surface of the APC.

There are two types of MHCs and so, of APCs.

- The so-called ***professional APCs*** are the innate-response macrophages and dendritic cells as well as the adaptive-response B cells, all of them cells of the immune system. When such a cell phagocytizes an external pathogen, it associates pieces of the antigens with MHC class II (***MHC II***) molecules and displays the complex on its surface.
- ***Non-professional APC***s include other nucleated cells in the body.[42] They are not phagocytes, but they nevertheless display class I MHC (***MHC I***) complexes of *internal* pathogens, such as viruses which have reproduced within the cell.

Professional APCs can display MHCs of both classes, depending on whether the pathogen is internal (MHC I) or external (MHC II).

41 A clone is not a simple copy, it is a set of copies sensitive to a specific antigen.

42 Reminder: red blood cells lose their nuclei.

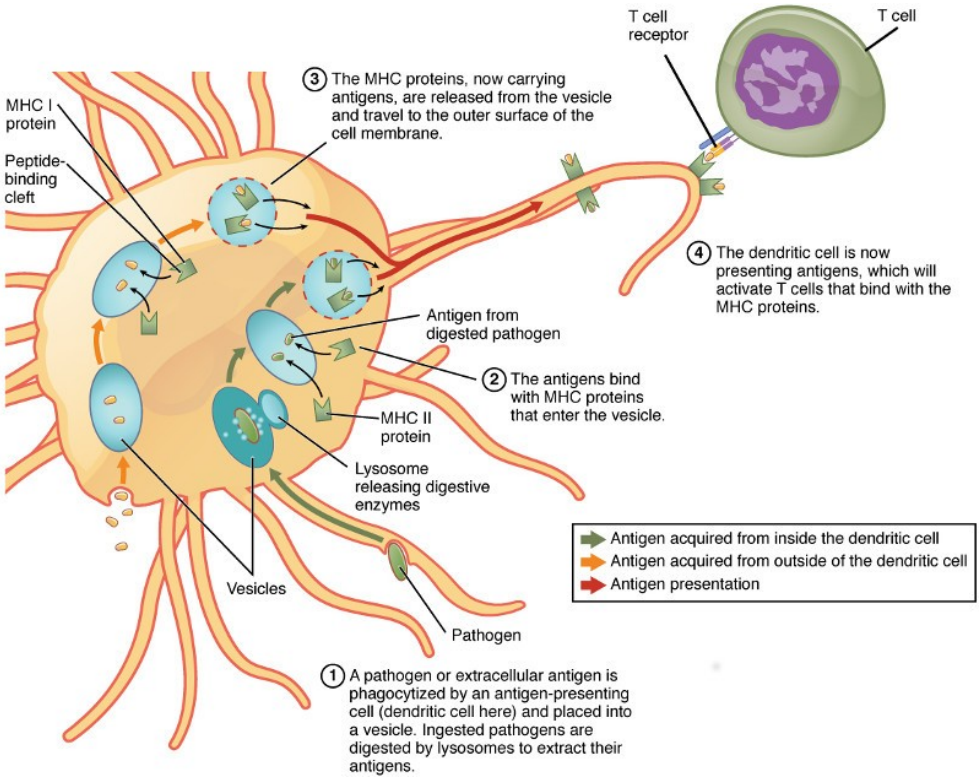


Figure 10.20: Antigen presentation, from Openstax College[43]

10.7.5. Adaptive immunity

Now for more details. I find this subject easier to understand by starting with B cells, which will leave them partly unexplained until T cells have been discussed.

Humoral response – B cells and antibodies

When a “naive” B cell leaves the bone marrow or the lymphatic system and binds to an antigen, its activation process has begun. B cells can be activated by unprocessed antigen, without need of any MHC. Part of the antigen is internalized, broken up and displayed on the cell's surface in an MHC II complex. When this is bound by a type of T cell called a Th2 cell (to be explained real soon), the B cell is completely activated. (Some B cells are T-cell independent and do not require such activation.) The B cell then is duplicated into sets of ***clones*** to make many B cells of two types – ***effector*** cells and ***memory*** cells. The effector cells, now called ***plasma cells*** (not to be confused with blood plasma, which is mostly water) release a form of their surface receptors called ***antibodies***, or ***immunoglobulins*** (abbreviation ***Ig***), into the environment.

The immunity conferred by antibodies is called ***humoral immunity***. Each antibody recognizes only the antigen specific to its parent B cell. When antibodies – immunoglobulins – encounter a pathogen carrying this antigen, they bind tightly to it via a lock-and-key mechanism based on their respective shapes and thus prevent the pathogen from doing any harm. They also signal phagocytes to absorb and kill the pathogen (opsonization again).

The memory cells wait around until they either die or are needed again to clone and produce more receptor and memory cells. Some of them remain available for years or even decades. When needed, they allow for a much more rapid response to subsequent infections, called ***secondary response***, as opposed to the initial, ***primary response***. In secondary response, B cells as plasma cells are already available for producing antibodies without going through all the rigmarole of APCs and being activated by a T cell. We will look at why this takes place later.

43 http://cnx.org/contents/FPtK1zmh@8.24:nhq46TFQ@4/The-Adaptive-Immune-Response-T.

Antibodies exist in five classes, imaginatively called IgA, IgD, IgE, IgG and IgM.

- Only IgM and IgD function as receptors on naive B cells; IgD remain on the B cells.
- IgM can leave the B-cell surface. They are the largest of the Igs, having 10 binding sites, whereas IgA has four and the others only two. So IgM is an excellent binder, especially during the early part of a primary response. In the latter part of the primary response, IgM can undergo a process of ***class switching*** in which it changes to a class IgG, IgA or IgE.
- IgG is the most common (80% of antibodies in serum) and is the most important antibody in secondary response. It also is the only one which can cross the placenta to protect the fetus.
- IgA has two forms. The eight-chain structure moves into mucous membranes and so is the only antibody to leave the interior of the body. The four-chain form remains in the blood.
- IgE is very rare. It serves to make mast-cell degranulation specific. In doing so, it contributes to allergies.

Cell-mediated response – T cells

Like B cells, T cells exist in some 10^{11} possible versions, each receptive to a specific antigen. This specificity depends both on the sequence of amino acids and on the 3D shape of the antigen-binding site. But T cells are more complex than B cells (which is why we left them until now), being of two types, one of which has sub-types.

Unlike B cells, T cells can not detect antigens directly; they can only detect those which are displayed on the surface of APCs. Just as there are two types of APCs, according to their MHC type, there are two types of T cells. Certain glycoproteins on T cells are called ***clusters of differentiation***, or ***classification determinants*** or simply ***CD***s. As the mature T cells leave the thymus, most have either CD4 or CD8, but not both, and so are called $CD4^+$ or $CD8^+$.

- CD4 is a co-receptor which enables so-called helper T cells, or ***Th*** cells, to recognize class II MHCs on APCs, including those on B cells.
- CD8 is specific to MHC I and to ***cytotoxic*** T cells, also called ***Tc*** cells.
- There is a third type, called ***Treg***, for ***regulatory T cell***, with CD4 and CD25.

Tregs are less well understood, but suppress immune response by other T cells in certain cases.

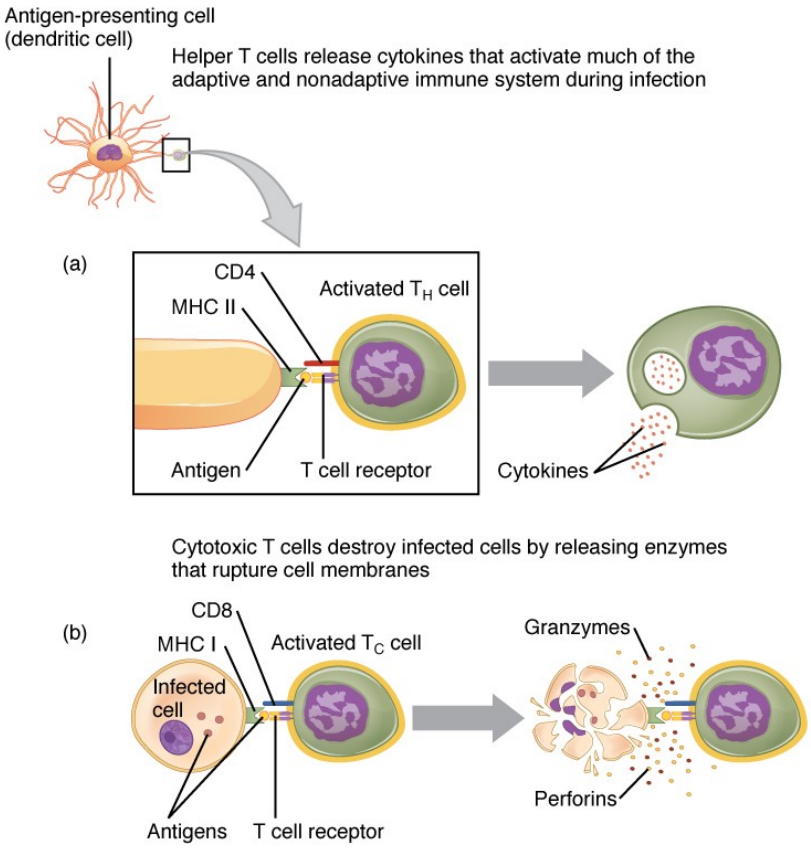


Figure 10.21: T-cell activation by APCs, from Openstax College[44]

Of the two principal types, those simpler to understand are the $CD8^+$ cells, called ***cytotoxic T cell*** or ***Tc*** cells when they are activated by antigens presented by MHC II APCs. As in the case of B cells, activated T cells multiply by mitosis into sets called clones and while some of these become memory T cells, awaiting the next infection, the others become effector T cells. Effector T cells destroy infected cells by inducing apoptosis, like NK cells. Since each antigen is broken up into pieces, it will likely produce a number of different types of Tc cells, all poised to wipe out any new appearance of the pathogen. This is the basis of ***immunity*** to a disease. Since Tc cells employ MHC I, which detect internal pathogens, notably viruses, Tc cells are essential to defense against viruses.

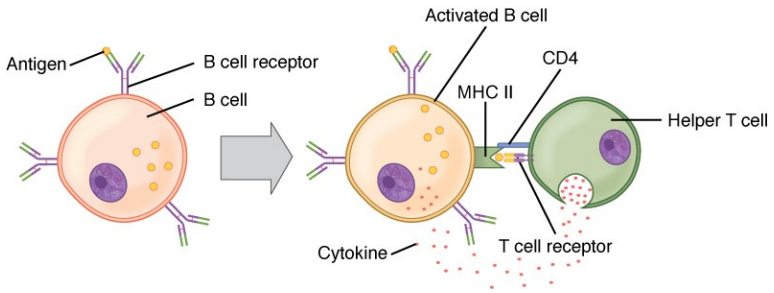


Figure 10.22: B cell activation, from Openstax College[45]

The other main type of T cell is the ***helper T cell***, or ***Th***, which exists in two versions, Th1 and Th2, the difference being mainly in the type of cytokines they secrete. ***Cytokines*** are short-distance signaling molecules. Those secreted by Th1 act as an alarm signal and promote phagocytosis. Alas, helper T cells are damaged by the human immunodeficiency virus (HIV).

Th2 is the one we have been putting off and which allows the B cell to do its job of distributing

44 http://cnx.org/contents/FPtK1zmh@8.24:nhq46TFQ@4/The-Adaptive-Immune-Response-T.

45 http://cnx.org/contents/FPtK1zmh@8.24:nhq46TFQ@4/The-Adaptive-Immune-Response-T.

antibodies. In order to have any effect, a Th2 cell must recognize its own antigen type on a B cell's class II MHC. When this happens, the Th2 cell secretes cytokines which, when detected by the B cell, complete activation of the B cell, so that it may clone to memory cells and antibody-emitting effector cells. A possible reason for the complexity of this procedure will be explained shortly.

10.7.6. Quick overview

Let's do a run-over of the ***humoral immune system***, the creation of antibodies[46]:

- A B cell of the *adaptive* immune system meets a pathogen of the same type as the B cell's membrane-bound immunoglobulin, phagocytizes it and presents its antigens on its surface in MHC II complexes.
- A phagocyte cell of the *innate* immune system, such as a dendritic cell, phagocytizes a pathogen. It also presents antigens from the pathogen on its surface in MHC II complexes.
- Both the dendritic cell and the B cell are now APCs for the specific antigen. These two steps could have occurred in either order.
- A T cell for the same type of antigen bumps into a dendritic cell, binds to the MHC II complex and becomes activated. It may then clone to memory and effector cells.
    - If the activated T cell is a cytotoxic Tc, it kills target cells by inducing apoptosis.
    - If the activated T cell is a a helper of type Th1, it emits regulatory cytokines.
    - If the activated T cell is a helper of type Th2, it may later meet our B cell and bind to its MHC II complex. It then release cytokines which complete activation of the B cell.
- The activated B cell clones itself into effectors and memory cells, the former being plasma cells which emit numerous immunoglobulins, or antibodies.
- The antibodies cling to any of their specific pathogens and render them harmless. At the same time, they tag them for phagocytosis.

Such is the case for an external pathogen. But some pathogens, like cancers, may occur internally or, like viruses, penetrate into the cell before being noticed. Since all nucleated cells may present MHC I complexes, these will be recognized by $CD8^+$ cells which are activated to cytotoxic T cells which will act to kill the offending (or offended) cell.

Once activated, all B and T cells duplicate to form clones of numerous effector cells and memory cells.

10.7.7. Why so complicated? – auto-immunity

Why do B cells have to go through a process of being activated by T cells (which have to be activated by APCs...) before producing antibodies in the primary response? One answer is to avoid auto-immunity.

Auto-immunity is when your immune system mistakes some essential part of you for a pathogen. This can lead to some really awful conditions like AIDS, lupus or *myasthenia gravis*. Since the receptors on B and T cells are the result of gene shuffling, many combinations will occur which could lead to auto-immunity. This is avoided in two ways:

1. Under the assumption that pathogens are rare within the bone marrow and the thymus, any B or T cells which activate inside them are killed before they can get out and do any harm.
2. The probability that either a B or T cell released into the body be an auto-immune cell is small (because of step 1), The process of requiring that a T cell "vet" the activation of a B cell through

46 Remember, we use the words immunoglobulin and antibody to refer to the same things.

the APC process means that the total probability of generating an auto-immune cell is something like the product of the individual probabilities and therefore very low indeed.

So the requirement that B cells be activated by their corresponding activated T cell is a way of avoiding auto-immunity. Nevertheless, however low the probability, some auto-immune diseases do occur ... alas.

11. What developmental biology tells us

Knowing about embryonic development is especially helpful in understanding the structure of the brain.

11.1. Fertilization, pre-embryonic development

Human pre-natal development traverses three stages:

- The first two weeks of human development are called the ***pre-embryonic*** stage;
- weeks 3-8, ***embryonic***;
- and after that, ***fetal***.

Let's start at the beginning.

Of the tens of millions of human sperm ejected during intercourse, millions are destroyed by the acid environment (pH 3.8) of the vagina or trapped by gluey cervical mucus. Thousands more are killed by uterine leukocytes.[47] The sperm follow the gradient of the chemical progesterone, which is released by the ***oocyte*** (egg). The surviving sperm usually meet the oocyte in the ***uterine*** (***fallopian***) ***tubes*** between the ovary and the uterus, since an unfertilized egg cannot live long enough to make the three-day journey along the tube. It is a question of force of numbers, as hundreds of sperm burrow through the oocyte's outer protective cover, the ***corona radiata***. Together, they release digestive enzymes from their tips to degrade both this layer and the inner layer, the ***zona pellucida***. Finally, one sperm may manage to fuse its cell membrane with that of the oocyte so that it can release its DNA-containing nucleus into the oocyte. Then the work of the sperm is finished, as there exist mechanisms to prevent more than one sperm from fertilizing the oocyte. The process by which the haploid oocyte and the haploid sperm form a diploid ***zygote*** is rather more complicated than this, but that is the result.

Some time after fertilization, *all* the male mitochondria in the embryo are destroyed, leaving only the maternal mitochondria. It is not known how male mitochondria are recognized, but a gene has been identified, cps-6, which is imported into the male mitochondria and breaks them down. Since suppression of this gene leads to increased mortality in these embryos, there is certainly an evolutionary cause for the destruction, but it is not yet known.[48]

The ***conceptus***, the zygote and its containing membranes, takes three days to reach the uterus. Along the way, mitotic ***cleavage*** increases the number of cells, called ***blastomeres***, but without increasing the total overall size. By the time the conceptus reaches the uterus, it is composed of sixteen compacted cells, together called a ***morula***. Mitosis continues, soon making about 100 cells arranged in a dense shell around a fluid-filled cavity called a ***blastocoel***. The conceptus is now called a ***blastocyst***. The cells of the outer shell are called ***trophoblasts*** and will form structures like the placenta. Within the cavity, other cells form an ***inner cell mass*** which will become the embryo.[49]

During this time, the inner mass is composed of ***totipotent***, then ***pluripotent***, ***stem cells***, which can differentiate to form any type of cell within the body.

47 Only strong sperm will make it. Force of numbers helps, too.

48 "How paternal mitochondria are destroyed in an embryo", https://whyevolutionistrue.wordpress.com/2016/06/24/paternal-mitochondria-are-destroyed-in-an-embryo/.

49 Information in these paragraphs on fertilization comes mainly from Wolpert (2011) and Openstax Anatomy and Physiology,http://cnx.org/contents/FPtK1zmh@8.25:FwQJfRAS@3/Embryonic-Development.

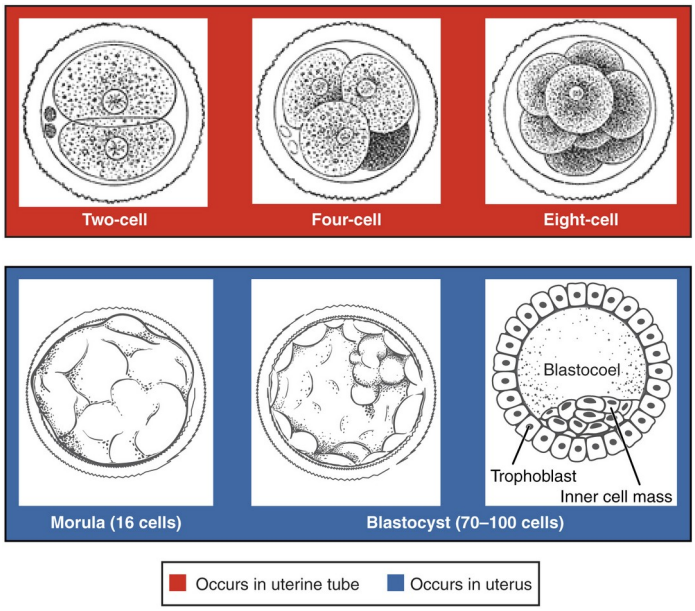


Figure 11.1: Pre-embryonic cleavages, from Openstax College[50]

After a week, if all goes well, the blastocyst will attach to the inner uterine wall, the ***endometrium***. In over half the cases, though, all does not go well and the blastocyst goes out with the menses. In successful ***implantation***, the blastocyst eats through the endometrium, which then reforms so as to surround the embryo. The implantation marks the end of the pre-embryonic and the start of the ***embryonic state***.

At the second week of embryonic development, the human zygote has developed into a two-layered embryonic disc contained between the ***blastocyst cavity*** (which will become the yolk sac) and the ***amniotic cavity***. The ventral (forward) layer against the blastocyst cavity is the ***hypoblast***. The dorsal layer against the amniotic cavity is the ***epiblast***.

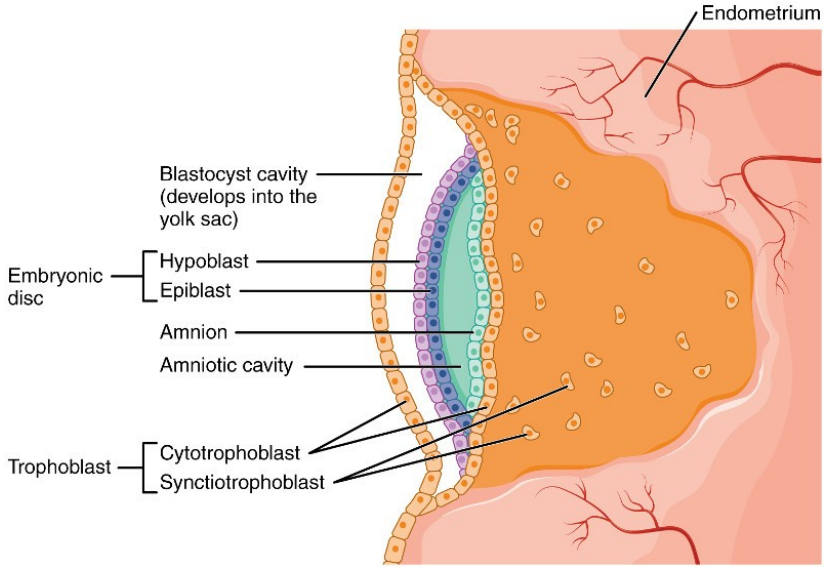


Figure 11.2: Human embryo before gastrulation, after Openstax College[51]

11.2. Gastrulation and embryogenesis – germ layer formation

At the third week, ***gastrulation*** takes place, converting the embryo from a two-dimensional disc into a

50 Openstax Anatomy and Physiology, https://cnx.org/contents/FPtK1zmh@8.25:FwQJfRAS@3/Embryonic-Development.

51 Openstax Anatomy and Physiology, https://cnx.org/contents/FPtK1zmh@8.25:FwQJfRAS@3/Embryonic-Development

complex three-dimensional structure formed of three germ layers. An indentation called the ***primitive streak*** forms along the dorsal (toward the back) surface of the epiblast. ***Growth factors*** produced by cells at the caudal (toward the posterior) end of the streak bring about cell multiplication. New cells migrate to the surface of the epiblast where they are specified as one of two new types, then migrate through the streak and form two new cell layers called ***germ layers***.

- One layer, called the ***endoderm***, pushes aside the hypoblast and comes to lie against the yolk sac. The endoderm will form the epithelial lining of the internal organs, among other things.
- A middle layer called the ***mesoderm*** is formed next to that. It will form the skeleton, muscles and connective tissues.
- The remaining epiblast cells become the third germ layer, the ***ectoderm***. It will form the integumentary (skin) and nervous systems.

In chordates (such as us), as the neural streak shortens and disappears, it leaves behind a rod-like structure called the ***notochord***. The notochord will later become the ***nucleus pulposus***, the viscous inner core of the inter-vertebral discs that can cause such excruciating back pain when they function badly.

The mesoderm along the notochord forms paired lateral bulges called ***somites***. Positional identity along this axis is furnished by our old friends the hox genes. As we have seen, these genes are expressed in the same order in the DNA as along the antero-posterior axis of the developing embryo. From the somites will develop the spinal column and its 33 vertebrae, as well as associated skeletal muscle.

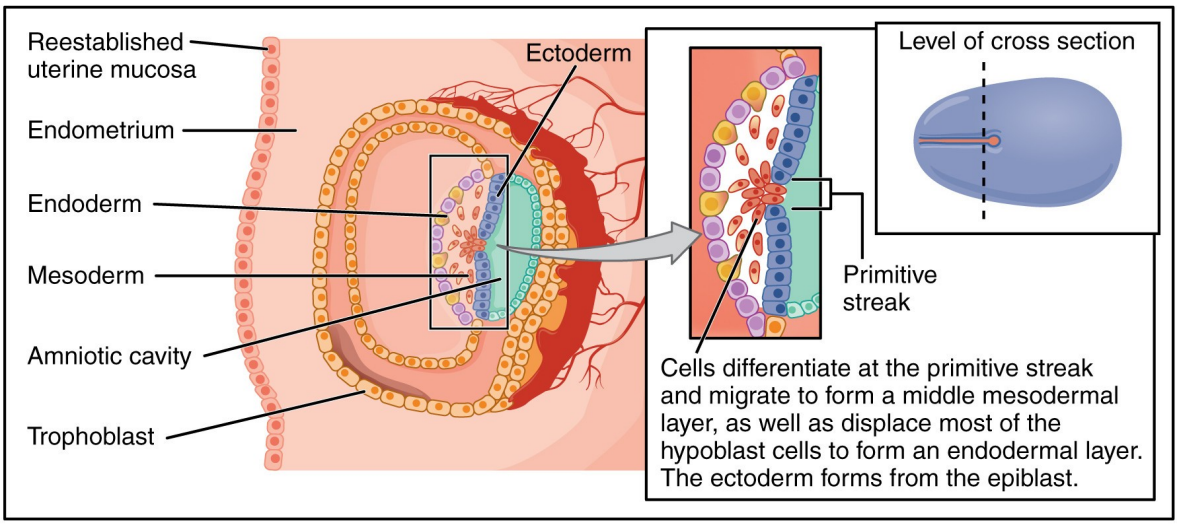


Figure 11.3: Gastrulation of the human embryo, after Openstax College[52]

Three mechanisms are important for these changes:

- Changes in cell shape are important in gastrulation and other processes. For instance, if a cell contracts on one side, it will become wedge-shaped. Joined to other cells with the same shape, an arc is produced, which is how a flat sheet of cells can bend. Such changes originate in the cytoskeleton.
- Cells have proteins on their surfaces which bind selectively to proteins on other cells, thus causing specific cells to adhere together. Different adhesive molecules cause different cells to adhere to one another.
- Cells can move relative to other cells by extending a long process called a ***filopodia***, which is

52 Openstax Anatomy and Physiology, https://cnx.org/contents/FPtK1zmh@8.25:FwQJfRAS@3/Embryonic-Development.

pushed out by elements of the cell cytoskeleton. The filopodia then move by a retraction mechanism similar to the one used by muscles to contract.

11.3. Neurulation – beginning of organogenesis and the nervous system

Soon after gastrulation, the rudiments of the CNS develop in the process of ***neurulation***. Some cells of the *ectoderm* differentiate into ***neurepithelium*** and form a thickened area of the dorsal ectoderm called the ***neural plate***. As shown in the figure, cells in the plate change shape and form a groove, the ***neural groove***. The sides of the groove constitute the ***neural folds***, which invaginate (grow out and come together to form a depression) and fuse, forming a ***neural tube***. Cells along the tube change their adhesive properties so that the tube separates from the plate. The entire CNS will develop from the neural tube walls. The posterior part of the neural tube is formed differently, from a rod of cells which develop an interior cavity.

As the neural folds fuse, some ectoderm at the edges of the neural plate is squeezed off and is then situated between the neural tube and the ectoderm. This is called the ***neural crest*** and is the source of the entire PNS.

Lateral bulges of the mesoderm form ***somites*** which will develop into much of the skeletal system and muscles.

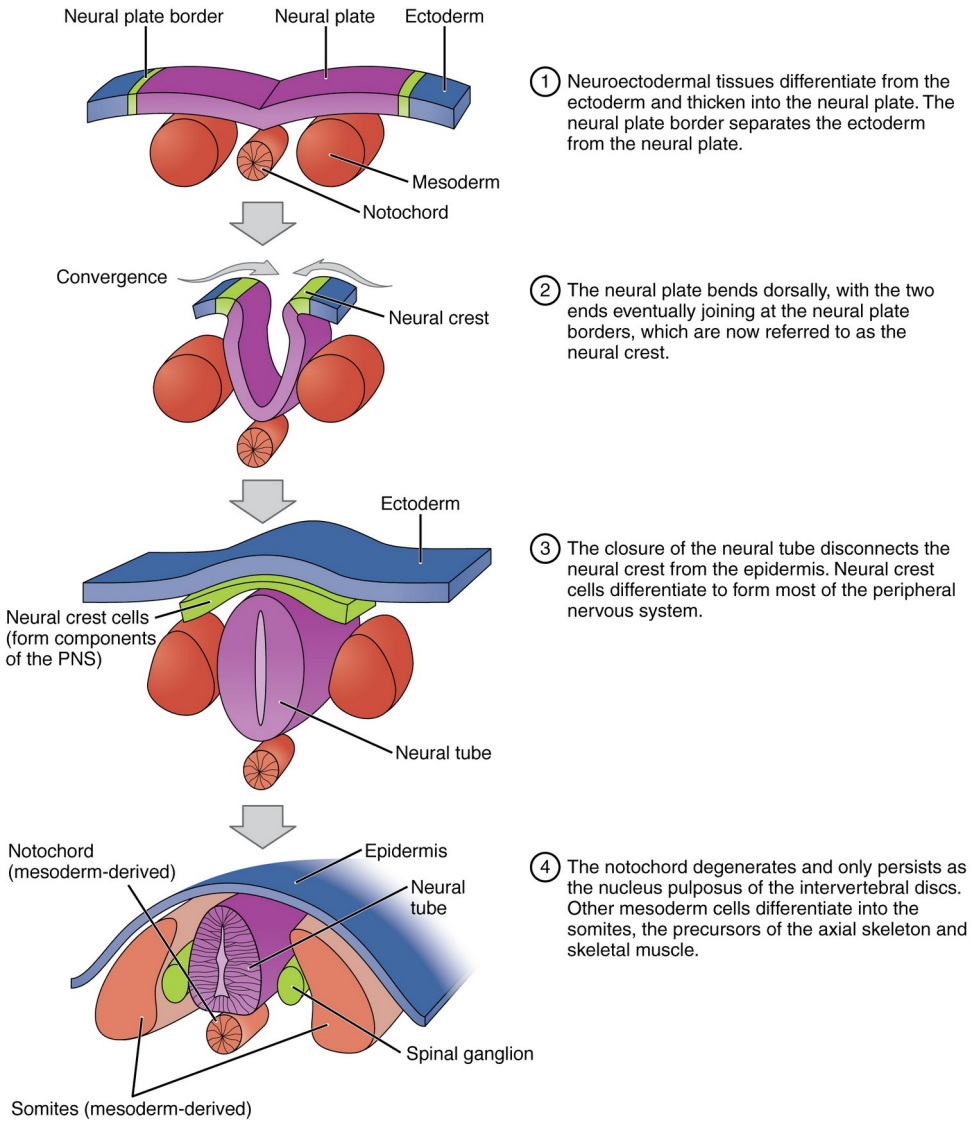


Figure 11.4: Neurulation forms the rudiments of the CNS and skeleton, from Openstax College[53]

11.4. Organogenesis

By eight weeks after conception, the rudiments of all the basic organs have been set up. This is called ***organogenesis***. Neurulation is the first important stage of organogenesis.

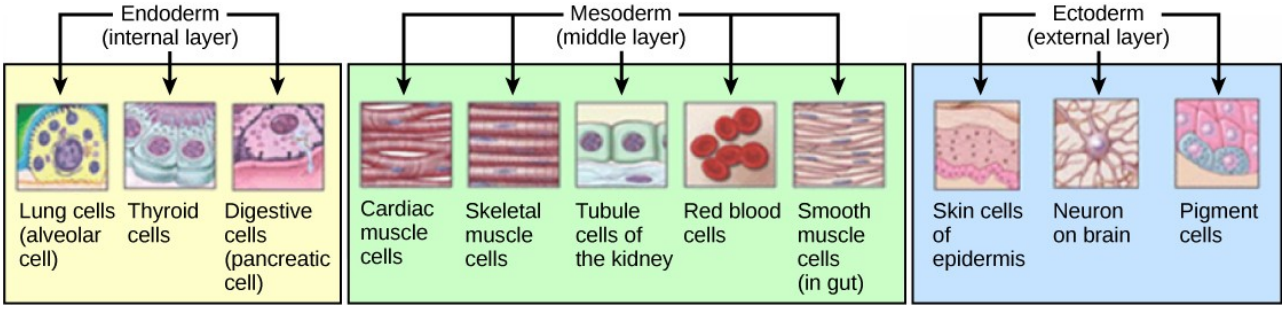


Figure 11.5: Development of the germ layers in development, from Openstax College[54]

The three germ layers develop into different tissues as shown in the figure. Not shown are the

53 Openstax Anatomy and Physiology, https://cnx.org/contents/FPtK1zmh@8.25:FwQJfRAS@3/Embryonic-Development

54 Openstax College, http://cnx.org/resources/cdd4d14f0c1cde804e5a84495390806c/Figure_43_05_04.jpg

development of bones from the mesoderm, or the development of the CNS from the ectoderm.

The following table shows a brief outline of embryonic development.

Week	Major events
4-5	The heart forms first as a tube, like the CNS, and starts beating around the beginning of week four. The liver starts to produce blood cells, a process which will later pass to bone marrow. Eye pits, limb buds and the beginning of the pulmonary system form.
6	Limb development starts in earnest.
7	Nostrils, outer ears and lenses form.
8	The major brain structures are in place. External genitalia are visible, but male and female are indistinguishable. Bone starts to take over from cartilage.

As it grows, the embryo folds so as to take on the familiar cylindrical shape, pointed at one end, with a primitive gut tube surrounded by the endoderm.

The organism is now at the stage of fetal development. From this point, we will restrict our interest to the consideration of nervous-system development and the brain.

12. What neuroscience tells us...

The ultimate goal of neuroscience – the science of the brain and nervous system and cognition[55] – is to understand the workings of the mind and of consciousness – with treatment of disease taken up along the way. Much is known, much is not. Some think the search to understand consciousness to be a fruitless quest.[56] So this chapter will be less conclusive than the others. We will look at an overview of the physical structure of the brain, the central and peripheral nervous systems, input from the sensory system and output to the motor system, how it works in terms of neuronal connections and some ideas on how memories are formed, And, of course, these subjects will again bring up our old friends – energy and communications. As a matter of fact, that is what the nervous system is all about – using energy to communicate.

Neurologists distinguish two interacting parts to the mammalian nervous system, the central and peripheral nervous systems. Lots of jargon is involved, not always the same in different contexts.

12.1. The central nervous system

The ***central nervous system*** (***CNS***) is contained within the brain and the spinal column, and so is surrounded by bone. It is composed of the following parts, from top to bottom.

- The ***cerebrum*** is the largest part and at the top. Much more on it later.
- The ***cerebellum*** ("little brain") is below the cerebrum and is concerned primarily with motor control.
- The ***brain stem*** (or ***brainstem***) lies between the spinal cord and the rest of the brain. It is the source of ten of the twelve cranial nerves and is a passage for nerves from the sensory and to the motor systems.
- The ***spinal cord*** runs from the brainstem down through the vertebral column and carries connections between the central and peripheral nervous systems.

The CNS is encased in bone -- the skull or the spinal column -- from which it is protected by the ***meninges***, composed of three layers. The outer (towards the cranium) tough layer is the ***dura mater***; the middle, spidery layer is the ***arachnoid layer;*** the inner, gentle layer (against the brain) is the ***pia mater.*** The space between the pia and the arachnoid is filled with cerebrospinal fluid (CSF). Blood vessels which supply the brain run along the pia before moving inward.

12.2. The peripheral nervous system

The ***peripheral nervous system*** (***PNS***) is composed of nerves and ***ganglia*** (singular ***ganglion***, a clump of neurons in the PNS) which lie (mostly) outside the spinal column. In the CNS, a similar clump of neurons is called a ***nucleus***. To make things more complicated yet, a bundle of axons in the CNS is called a ***tract***; in the PNS, a ***nerve***. The PNS has two divisions:

- The ***somatic nervous system*** (or ***sensory-somatic***) does conscious control, sending commands from the CNS to voluntary muscles in order to control body movements. It receives information from the body – the skin, skeletal muscle and sense organs.
- The ***autonomic nervous system*** (***ANS***), or ***visceral PNS***, controls the glands, heart and

55 Cognition is "the mental action or process of acquiring knowledge and understanding through thought, experience and the senses." (Wikipedia)

56 Such people include linguist and political observer Noam Chomsky and the researcher quoted as saying, "If the human brain were simple enough to understand, we would be too simple to understand it". (Quoted in Openstax *Anatomy and physiology*.

involuntary muscles, usually without our being conscious of it. It is in turn considered in two parts:

- The ***sympathetic nervous system***[57] prepares the body for immediate action, e.g., for defense ("fight or flight"), by shutting down processes that can be dispensed with temporarily, like digestion, and augmenting processes like heartbeat and blood pressure. Sympathetic NS nerves originate in the thoracic and lumbar regions of the spinal cord.
- The ***parasympathetic nervous system*** controls normal, resting homeostasis. It originates in the cranial nerves and the sacral region of the spinal cord.
- Many scientists consider a third component, the ***enteric nervous system***, which manages digestion.

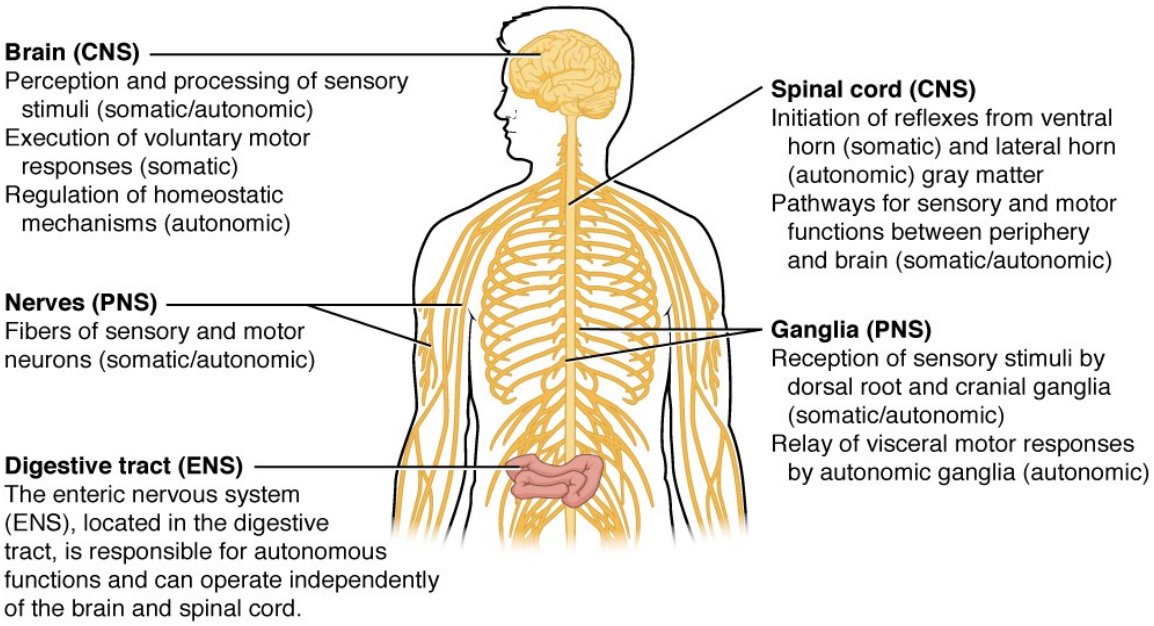


Figure 12.1: Somatic, autonomic and enteric nervous systems, from Openstax College[58]

The two nervous systems are articulated in or around the spinal cord, which can be considered the bridge between the two, and hence between the brain and the body's motor system.

57 Quora says it's called "sympathetic" because all the ganglia concerned have to work together synchronously.

58 Openstax Anatomy and Physiology, https://cnx.org/contents/FPtK1zmh@8.25:yEs2p8R_@6/Basic-Structure-and-Function-o.

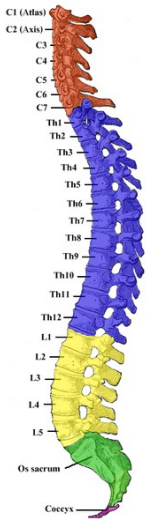


Figure 12.2: Regions and segments of the human spinal cord, after Gray's Anatomy via Wikimedia.[59] *Regions are cervical (red), thoracic (blue), lumbar (yellow), sacral (green) and coxxygeal (red, at the bottom).*

Thirty-one pairs of ***spinal nerves***, bundles of axons which enter or leave the spinal column at different levels, pass through notches between adjacent vertebrae. They are labeled by the region and the number of each vertebra. Spinal nerve pairs C1 to C8 originate in the cervical region; T1-T12 in the thoracic; L1-L5 in the lumbar, S1-S5 in the sacral; and one pair in the occipital bone. Each one connects to parts of the body at that level or below it: The top connects to muscles and sensory receptors from the neck; the bottom, to the toes. The diagram, Figure 12.2, shows vertrebrai, not nerves.

Afferent (incoming), sensory axons enter the spinal cord by the ***dorsal root*** and their cell bodies are grouped just outside the root in ganglia, the ***dorsal root ganglia***.

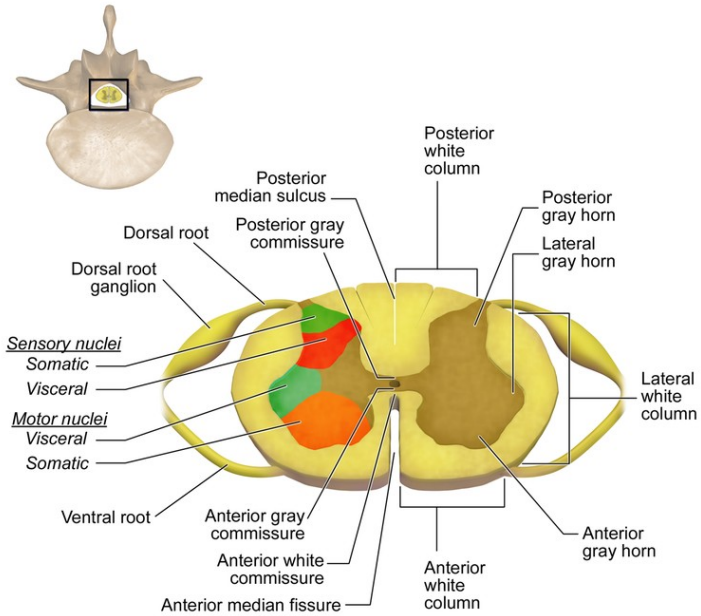


Figure 12.3: Spinal cord section, by "BruceBlaus" via Wikimedia Commons[60]

Efferent (outgoing) axons leave by the ***ventral root***, but once outside, are bundled in the same spinal nerves as the afferent axons. Bodies of motor neuron cells are inside the spinal cord.

59 https://commons.wikimedia.org/wiki/File:Gray_111_-_Vertebral_column-coloured.png

60 Spinal cord sectional anatomy. https://commons.wikimedia.org/wiki/File:Spinal_Cord_Sectional_Anatomy.png.

In addition, there are twelve (or thirteen, according to definition) pairs of ***cranial nerves*** which emerge directly from the brain and brain stem. They are numbered by Roman numerals, CNI-CNXII. Among them, the terminal, olfactory and optical nerves emerge from the cerebrum, the others from the brain stem. They also are considered part of the PNS.

Muscle activation spans a range from involuntary, automatic movements (e.g., blood vessel contraction or pupil dilation), through conscious but unplanned reflex movements (withdrawal from burning objects) and on to planned, conscious movements (walking). All require that input from sensory receptors in the region concerned be coordinated with movement planning in order to adjust and refine control. Note that simple reflex movements like knee jerks depend only on connections within the spinal column and their input never reaches the brain.

12.3. Cellular components of the brain

12.3.1. Neurons

A ***neuron*** possesses a cell body, or ***soma***, and various organelles, including a nucleus and mitochondria, like almost any other eukaryotic cell. In addition, a neuron possesses a "tree" of input branches called ***dendrites*** and generally one long output branch called an ***axon***, usually terminating in a number of smaller axon branches. Dendrites and axons together are referred to as ***neurites***. Chemical signals called ***neurotransmitters*** are passed from the axon terminal of one neuron across the gap, called a ***synapse,*** separating it from another neuron's dendrite terminal. If the second neuron receives a sufficiently great chemical signal, an action potential is created (as explained in chapter 7) which passes down through the cell's axon and out to the synapse to another neuron, where a chemical signal again is released. This process is then repeated. Through multiple dendrite and axon terminals, one neuron can communicate with many others to form a network. This is the basis of neuronal function.

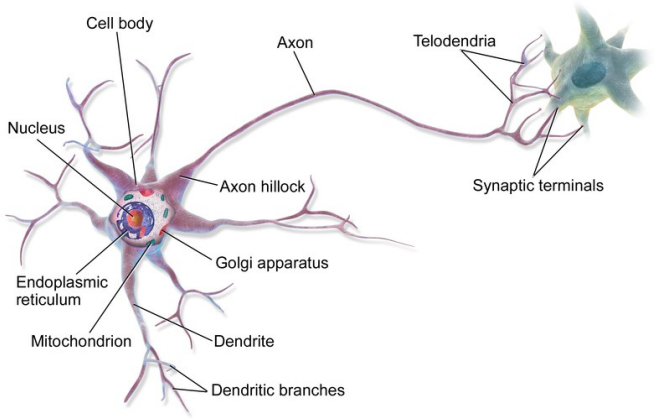


Figure 12.4: A multipolar neuron, by BruceBlaus via Wikemedia Commons[61]

Neuroscientists classify neurons in different ways.

The simplest distinction simply classes neurons by their number of neurites: unipolar, if one; bipolar, if two; multipolar, if more than two, like the above. In the cerebral cortex, the two principle types of neurons, as defined by the structure of their neurite trees, are ***pyramidal*** (triangular) cells, with one principal neurite running toward the outer and one toward the inner side of the cortex, and ***stellate*** cells, with many projecting neurites. Dendrites may be spiny (complicated) or not (aspinous). Neurons may be ***projection neurons*** (Golgi type I), projecting to farther parts of the brain, or ***local circuit neurons*** (Golgi type II), sticking around home. Pyramidal cells tend to have long dendritic trees and so

61 http://en.wikipedia.org/wiki/File:Blausen_0657_MultipolarNeuron.png

are projection neurons.

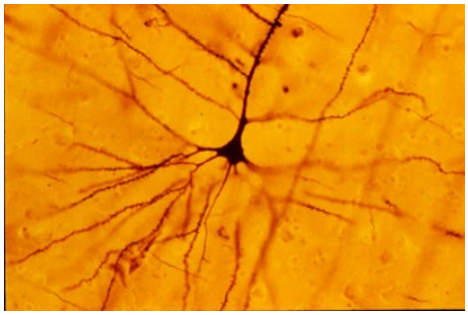


Figure 12.5: Pyramidal cell, from Wikimedia Commons[62]

Neurons are also classified according to the neurotransmitter they use. For instance, cholinergic neurons use the neurotransmitter acetylcholine.

Our senses depend on detecting objects in the external world and use receptors to do this. A receptor is generally a gated receptor, meaning that some event causes the receptor to open an ion channel. Here are some examples of such events:

- light energy (photons) on the photoreceptors of the retina;
- sound energy (pressure waves in the air) on the ear drum and the auditory cilia;
- stretching of the skin detected by somatosensory mechanoreceptors in the dermis;
- chemical substances on olfactory receptor cilia in the nose or on the taste buds of the tongue;
- binding of a specific substance (neurotransmitter) to the exterior part of the receptor ion channel (in communication between neurons);
- electric potential on voltage-dependent sodium channels (leading to depolarization of the cell).

Some neurons transmit output to the motor system, where different axon terminals activate sets of muscle fibers called ***motor units***.

In neurons, a signal is generated when a neurotransmitter molecule stimulates a ligand-gated channel specific to that neurotransmitter. The neurotransmitter may be excitatory or inhibitory.

- An ***excitatory*** neurotransmitter contributes to forming an action potential by depolarizing the cell, as already described.
- An ***inhibitory*** neurotransmitter opens either a Cl^- or a K^+ channel. Either Cl^- flowing into the cell or K^+ flowing out reduces the membrane potential, which is said to be ***hyperpolarized***, thereby reducing the probability of forming an action potential.

Receptors are also of two types according to their functioning.

- Receptors such as the ligand-gated ion channels we have seen, which let an ion pass through a pore in the same protein as the receptor, are called ***ionotropic***.
- Some receptors do not open a pore or allow an ion to pass. Instead, when the neurotransmitter, called the ***first messenger***, binds to the extracellular side of the receptor, the intracellular side causes a ***G protein*** to activate an ***effector protein***. The effector, which is an enzyme, causes generation of a molecule called a ***second messenger***, a messenger internal to the cell. The second messenger may bring about other events, often multiple or cascading. Such receptors are called ***metabotropic***. An example of a second messenger is cAMP, which we met in discussion of the lac operon, and which is generated by the effector adenylyl cyclase.

62 https://commons.wikimedia.org/wiki/File:GolgiStainedPyramidalCell.jpg.

More later on G proteins and cAMP.

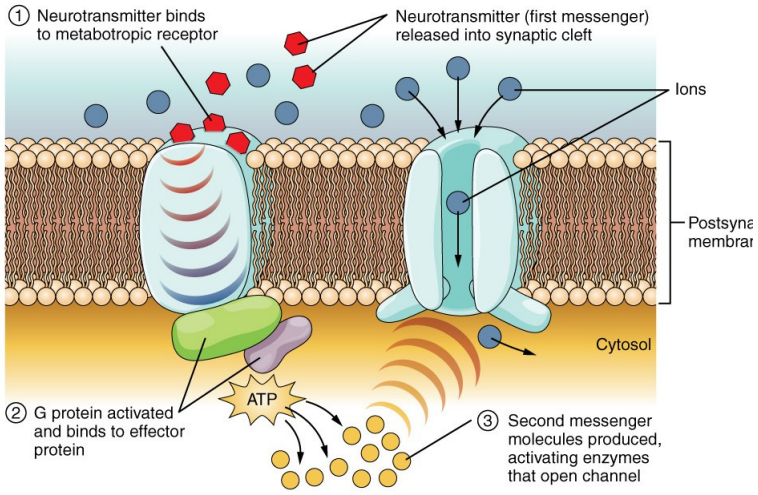


Figure 12.6: Metabotropic receptor, modified after Openstax College[63]

If the net result is excitatory, it may – along with other EPSPs – generate an action potential which flows down the neuron and along the axon, the output branch. Long axons are usually wrapped in a myelin sheath, which allows the signal to travel much faster than without it. There are breaks in the sheath called ***nodes of Ranvier*** where high Na^+-density, low threshold voltage-gated channels are activated to regenerate the action potential, acting as amplifiers of the action potential. Since the action potential jumps from node to node rapidly, this is called ***saltatory*** (jumping) conduction.

On arriving at the end of the axon terminal, the action potential activates a voltage-gated channel which allows Ca^{2+} to enter the terminal. These ions cause vesicles containing the appropriate neurotransmitter to fuse with the cell walls and release the neurotransmitter (***exocytosis***) across the postsynaptic cleft and onto the postsynaptic receptor on a dendrite of another neuron. There, the process may start all over again. Exocytosis does not depend on the presence either of Na^+ or K^+ but only on Ca^{2+} from voltage-gated channels.

Ca^{2+} is normally removed by several mechanisms, but rapid, repetitive presynaptic firing can produce an excess of Ca^{2+} and this in turn can lead to ***synaptic potentiation***, in which the EPSP remains enhanced (stronger) for a period of minutes or hours, a simple form of memory. But if this leads to a depletion in available synapric vesicles, the result may be ***synaptic depression***, with decreases EPSP amplitude,

Vesicles contain approximately 5000 neurotransmitter molecules of which they release all each time exocytosis takes places. Therefore exocytosis of a synaptic vesicle produces what is called a ***quantal synaptic potential***, in approximately fixed increments. Increased Ca^{2+} inflow increases the number of vesicles which release their contents into the synaptic cleft. Fusion of vesicles and the cell membrane is energetically unlikely and must be brought about by special fusion molecules called ***SNARE***[64] ***complexes*** which link to both. SNAREs are conserved across life forms "from yeasts to humans."[65]

63 https://cnx.org/contents/FPtK1zmh@8.24:p74vr6PZ@3/Communication-Between-Neurons

64 Soluble N-ethylmaleimidesensitive factor attachment receptors.

65 Kandel (2013), 278.

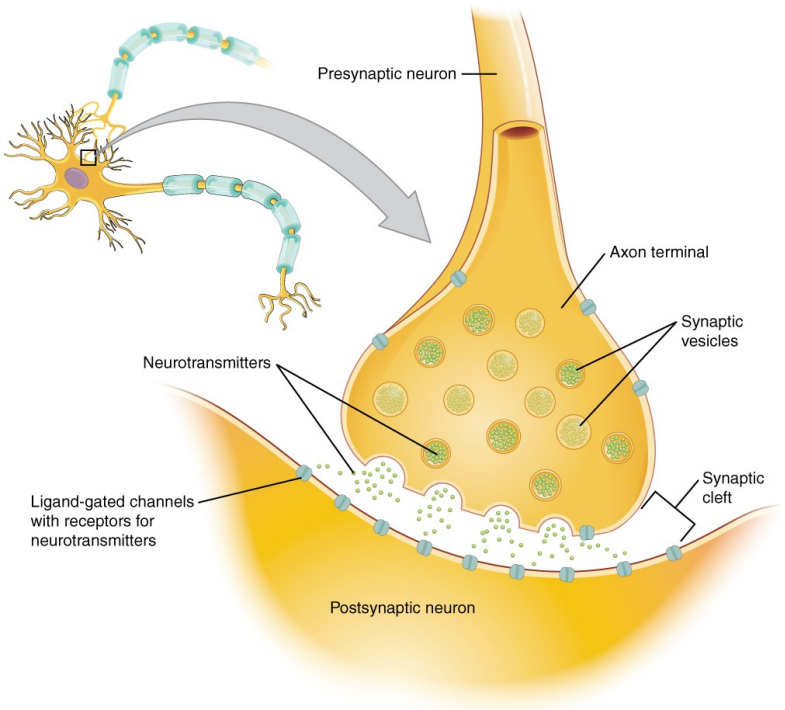


Figure 12.7: Chemical synapse between neurons, from Openstax College[66]

Quick review:

> *Voltage*-gated channels in the presynaptic terminal allow entry of Ca^{2+} ions, which induce release of a *chemical* neurotransmitter. On arriving at the postsynaptic terminal, the neurotransmitter opens a ligand-gated channel which may induce an *electrical* action potential. So a presynaptic electric signal has been linked to a chemical signal which is converted back into an *electric* signal in the postsynaptic terminal. Electricity to chemistry and back to electricity. In this way, electrochemical signals are propagated from one neuron to another or others, setting up "currents" of communication in the nervous system. These currents or circuits are the basis of what goes on in the brain – reflexes, emotions, thoughts, planning – the whole shebang.

12.3.2. Glia

There are about 100 billion neurons in the brain with an average of 1000 or so synapses each, impressive numbers. But there are anywhere from two to ten times that many other cells, called ***glial cells*** or ***glia***.[67] The word glia comes from a Greek word for "glue" and that was once thought to be the function of glial cells, to glue the neurons together. Glia are essential for the proper functioning of neurons.

Glia come in six types. The following four are found in the central nervous system (CNS).

- Star-shaped ***astrocytes*** once were considered simply a support system for neurons, but that view has changed. They surround neuronal synapses and so can control their local chemical concentrations. They are responsible for the ***reuptake*** of neurotransmitters left around after synaptic communication. By surrounding the arterioles and capillaries, they set up the ***blood-brain barrier*** (***BBB***), which uses active-transport mechanisms to limit what molecules can pass from the blood into the CNS. They allow in glucose and amino acids, for instance, but deny

66 https://cnx.org/contents/FPtK1zmh@8.24:p74vr6PZ@3/Communication-Between-Neurons

67 O'Shea, 29, 37.

passage to fats and other things, which also limits the passage of nutrients or medications to the brain. It has been found that astrocytes also possess neurotransmitter receptors and so can receive information from neurons and act on it. More on that in a moment.

- ***Oligodendrites*** (with few branches, “oligo” meaning “few”) have processes (projections of tissue) which surround up to 30 axon segments with myelin sheaths.
- ***Microglia*** act as phagocytes, surrounding and digesting damaged cells or pathogens. They function as the immune system of the brain.
- ***Ependymal cells*** line the ventricles of the brain and, along with the choroid plexus epithelial cells in certain ventricles, filter plasma to provide ***cerebrospinal fluid*** (***CSF***), which they cause to circulate throughout the CNS.

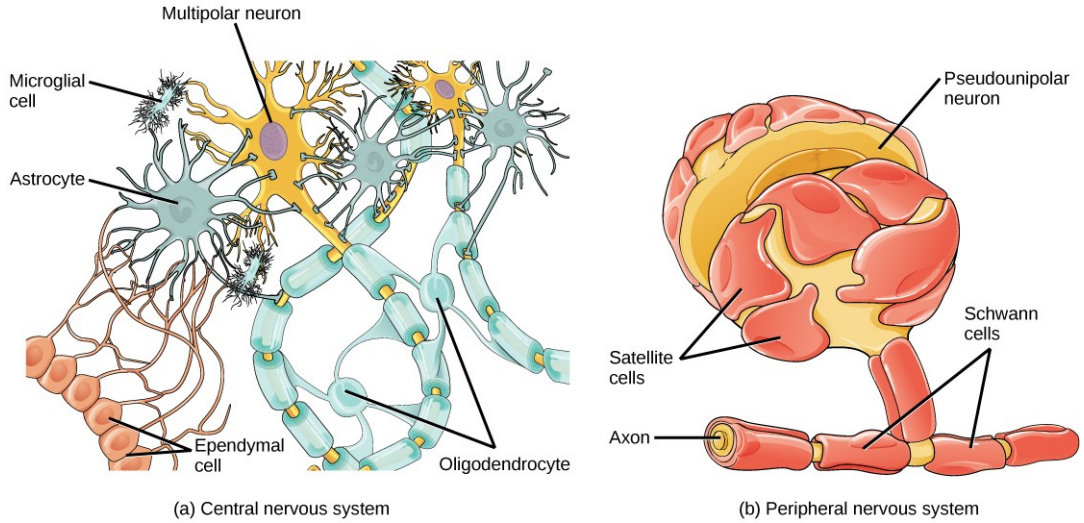


Figure 12.8: Glial cells, from Openstax College[68]

Two other types of glia are found in the peripheral nervous system (PNS).

- ***Satellite cells*** surround cell bodies in ganglia and provide support similar to that of astrocytes in the CNS.
- ***Schwann cells*** are similar to oligodendrites, providing myelin sheaths for axons, but one Schwann cell surrounds only one axon and does not have multiple processes.

Astrocytes are in close contact with the synaptic cleft and can share information in several ways.

- On the one hand, they contain neurotransmitter receptors which receive information from the synapse, but they do not generate action potentials. On the other, by secreting substances which change the chemical composition of the synapse, they can have an influence on synaptic events.
- Transporters in the astrocytes' membrane can quickly absorb neurotransmitters, clearing the synapse, again regulating synaptic activity.
- Astrocytes communicate among themselves by means of ***gap junctions***, which can be seen as tunnels between one astrocyte and another.

Through gap junctions, astrocytes exchange such ions as Ca^{2+}, or molecules like glucose or lactate. Glutamate released by a presynaptic neuron terminal and received by an astrocyte causes increased Ca^{2+} concentration, and these ions are passed through the gap junctions and on to nearby astrocytes. This flow can lead to a Ca^{2+} wave propagating across numerous astrocytes and eventually influencing

68 https://cnx.org/contents/FPtK1zmh@8.25:mYoZvS9p@3/Nervous-Tissue.

nearby neurons.[69]

K^+ ions released by firing of action potentials in the neuron are absorbed by the astrocytes and either stored locally or released far from the synapse.

In response to glutamate released by a neuron's presynaptic terminal, astrocytes may in turn release either more glutamate, strengthening the synapse, or GABA, inhibiting it. In this manner, astrocytes can modulate synaptic activity by emission of such ***gliotransmitters***. One of these is D-serine, which is a regulator of NMDA receptors. This would give astrocytes a role in memory (long-term potentiation). (More on NMDA receptors and LTP in section 12.12.5.)

So a synapse can be seen as not only a communication route between two neurons, but between the neurons and neighboring astrocytes – and their neurons. Since the release of a neurotransmitter like glutamate from the presynaptic neuron terminal stimulates a reaction not only in the postsynaptic neuron terminal but also in the neighboring astrocytes, such a synapse may be referred to as a ***tripartite synapse***.

Astrocytes also convert glutamate absorbed by reuptake to glutamine, which they then feed back to the neurons to be reconverted to glutamate for use by the neuron.

Since astrocyte processes are in contact with capillaries, by detecting glutamate from presynaptic terminals, they also can regulate the flow of energy (blood glucose) to the neurons, in a sort of *ménage à trois*. This again allows them to influence neuronal activity.

The bi-directional communication between neurons and astrocytes leading to participation by the latter in synapse activity and energy supply to neurons has led in recent years to a new model of glial cells, one in which glial cells form not just a support system for neurons, but participate actively in brain activity.

Recent experiments have shown a greater importance of the role of glial cells in cerebral plasticity. It is thought that excited neurons emit neurotransmitter all along an axon and this signals adjacent oligodendrytes to start the formation of a myelin sheath along the axon. Also, perinodal astrocytes at nodes of Ranvier can inhibit action of the enzyme thrombine, which inhibits adhesion of myelin to an axon. In this way, oligodendrytes and perinodal astrocytes together can control the existence and thickness of the myelin sheath as well as the size of the nodes of Ranvier, thus influencing the speed of propagation of an action potential in the axon. Adjustment of speed can promote synchronization of signals arriving in the cortex from different regions and thereby result in improved motor function, learning and memory. Such effects have been observed in experiments and suggest a dynamic myelin structure.[70]

12.4. Quick overview of the CNS

Before getting into the details, let's consider some principle elements of the CNS, from caudal (tail or bottom) to rostral (top or front). Handling of sensory information and motor control from and to the skin and muscles is divided into two parts.

The ***spinal cord***, visualized in four regions – cervical, thoracic, lumbar and sacral – handles I/O to and from the skin, joints and muscles of the limbs and trunk

The ***brain stem*** similarly handles sensory information from skin and muscles of the head and motor control to head muscles. It serves as information bridge between the brain and spinal cord, and regulates levels of arousal and awareness through the ***reticular formation***.

- The ***medulla oblongata*** handles vital autonomic functions such as digestion, breathing and heart

69 Agid and Magistretti, 57; Kandel (2013), 95.

70 Regulation of myelin structure and conduction velocity by perinodal astrocytes. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6243273/. Also, Pour la science, no. 511, May 2020.

rate.

- The ***pons*** passes information about movement from the cerebral hemispheres to the cerebellum.
- The ***midbrain*** handles sensory and motor functions such as eye movement and coordinates visual and auditory reflexes.

The ***cerebellum***, which is connected to the brain stem by fiber tracts called peduncles, regulates movement and motor skills.

The ***diencephalon*** is in two parts.

- The ***thalamus*** receives information destined for the cerebral cortex from the rest of the CNS. It is the dispatcher of the brain.
- The ***hypothalamus*** regulates autonomic, endocrine and visceral functions. It is the brain's gateway to the endocrine system via the pituitary gland.

The ***cerebrum***, divided into two hemispheres, is composed of the outer cerebral cortex and deeper structures:

- The ***basal ganglia*** participate in the regulation of motor performance;
- the ***hippocampus*** is essential to memory storage;
- the ***amygdaloid nuclei*** (or ***amygdala***) coordinate autonomic and endocrine responses of emotional states.

12.5. Growth and development of the brain

Some knowledge of the development of the nervous system is essential to understanding the structure of the brain.

12.5.1. Development of the nervous system

The anterior neural tube (discussed in section 11.3) develops into the brain. It is first differentiated into three sac-like ***primary vesicles***, from front to back (rostral to caudal):

- the ***prosencephalon*** (forebrain)
- the ***mesencephalon*** (midbrain)
- the ***rhombencephalon*** (hindbrain), connected to the caudal neural tube.

As the prosencephalon begins to differentiate, two pairs of secondary vesicles grow on either side:

- the ***optic vesicles***, which will eventually become the optic nerves and the retinas (so the retina is part of the brain); and
- the ***telencephalic vesicles***, or ***telencephalon***.

The remaining unpaired part of the prosencephalon is called the ***diencephalon***, or “between brain”. The telencephalic vesicles grow out, then bend back over the diencephalon. From them grow another pair of vesicles, the ***olfactory bulbs***. Cells within the telencephalon develop, forming new structures and axon systems.

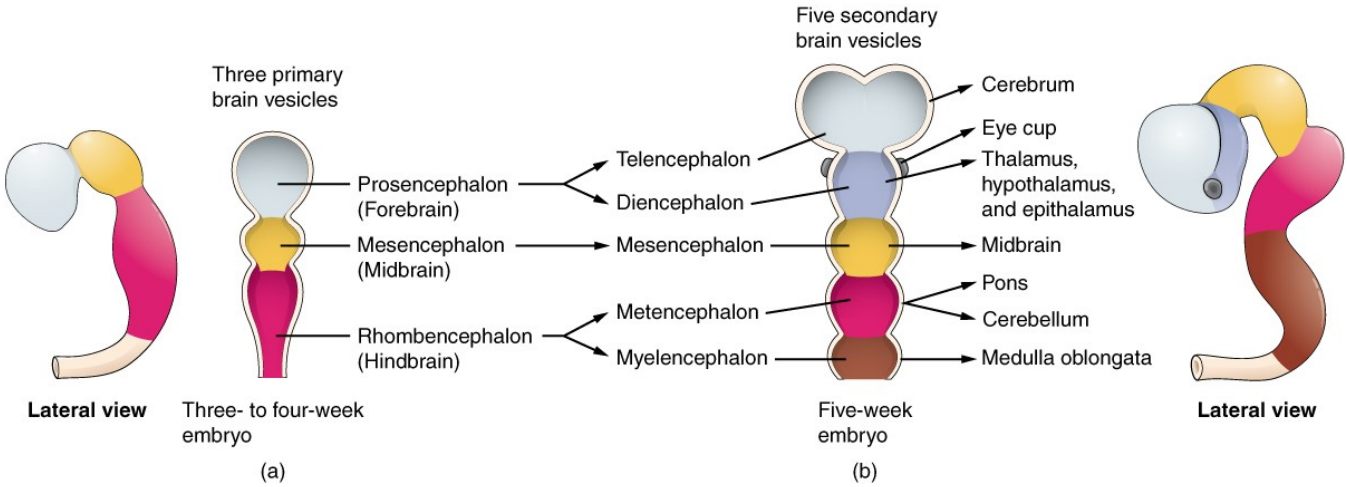


Figure 12.9: Brain vesicle development, from Openstax College[71]

Spaces remain between the sides of the telencephalon and the diencephalon; they will fill with ***cerebrospinal fluid*** (***CSF***) and become the ***ventricles*** of the brain.[72] The neurons which will develop within the gray matter of the telencephalon will form the ***cerebral cortex*** and the ***basal telencephalon***. The diencephalon will differentiate into the ***thalamus*** and the ***hypothalamus***. Axons from the developing forebrain will extend to connect with other parts of the nervous system.[73]

The hindbrain develops into the ***pons***, ***medulla oblongata*** and ***cerebellum***. In a coronal (side to side) section of the brain, it is easy to see how the telencephalon has grown down laterally to the diencephalon. The ventricles are also visible as dark areas.

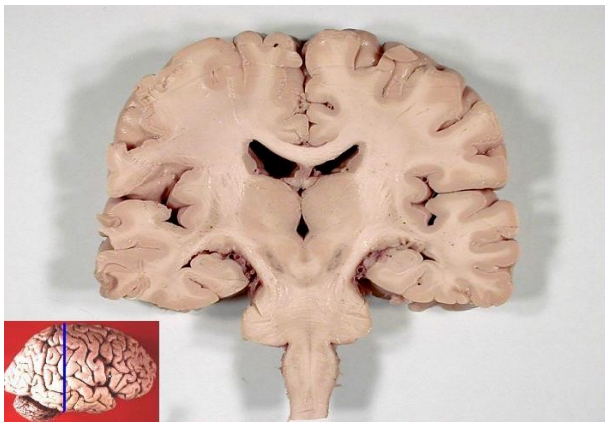


Figure 12.10: Coronal section of human brain, from John A Beal, via Wikimedia Commons[74]

The following diagram shows a somewhat more complete schema for the development of the human brain. The examples of development of germ layers are quite incomplete.

71 https://cnx.org/contents/FPtK1zmh@8.25:sDe94uo3@3/The-Embryologic-Perspective

72 Don't confuse vesicles, such as the prosencephalon or mesencephalon, with ventricles, the open spaces filled with CSF.

73 This brief summary is based on Bear, 178-192.

74 https://commons.wikimedia.org/wiki/File:Human_brain_frontal_(coronal)_section.JPG#globalusage. Looks a bit like the Hulk, doesn't it?

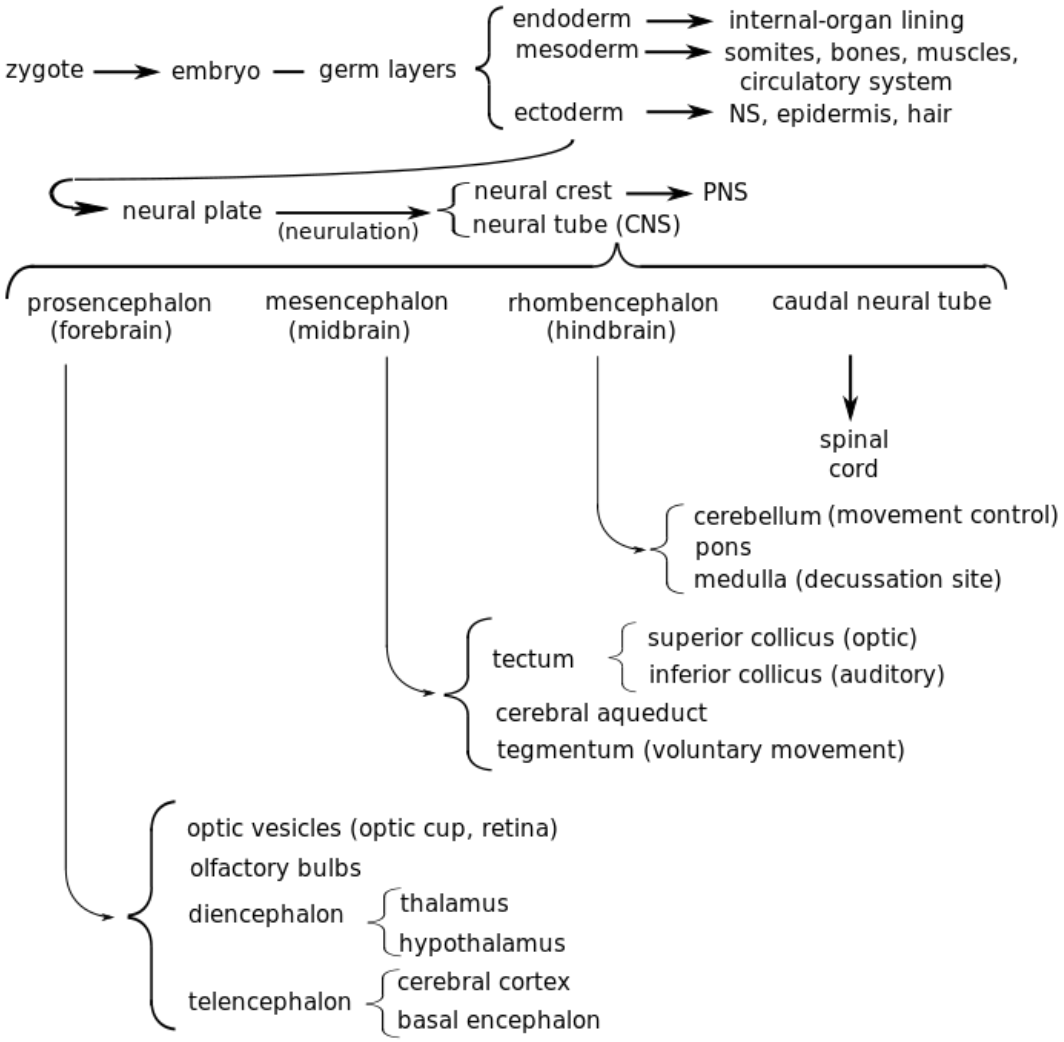


Figure 12.11: Schematic diagram of human brain development, by author after Bear et al.

Now let's look at how all this works.

12.5.2. Overall brain structure and evolution

The human brain weighs about 1.5 kg and contains on the order of 100 billion (10^{11}) neurons, each with an average of perhaps a thousand connections. The brain also includes the retinas of the eyes and extends down to the spinal column. It consists of an inner and evolutionarily older part, the ***mesocortex*** , which is covered over by the cortex, or ***neocortex***. The neocortex is about 2500 cm^2 (50 cm on a side) if spread out, but is compressed like a wadded-up piece paper so it contains creases called ***sulci*** (singular, ***sulcus***), deeper ones called ***fissures*** and bumps called ***gyri*** (singular, ***gyrus***).

Over the last two million years of evolution, the size of the hominid brain has almost tripled. The brain has not just grown, it has changed its form. There are no direct fossil records of brains, only skeletal craniums which may indicate brain size and, sometimes, the shape of the cortex. It seems, though, that as hominid brains increased in size, the cortex grew relatively larger and was reorganized in a way that facilitated emerging cognitive abilities, e.g., language. All this is the subject of ***paleoneurology ,*** a whole domain of study in itself and beyond the scope of our considerations.

Following the methods of geologists and biologists who learn about the past by studying the present, we can deduce Information about evolution by comparing the brains of different contemporary animals. The less-developed brains of animals like lizards possess only some of the components

found in mammal brains. In particular, the neocortex which covers all the rest of the mammal brain is non-existent or much more rudimentary in "lower" animals such as reptiles, so the lower part of the human brain has been called the "reptile brain". That is not to say it does not have essential functions, because it certainly does.

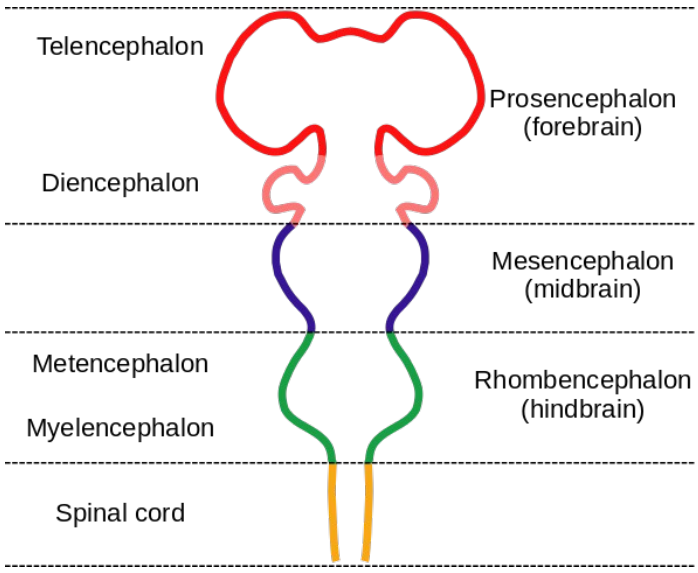


Figure 12.12: Embryonic brain parts, by "Nrest" via Wikimedia Commons[75].

The brain contains a fairly large number of functional elements. Today, brain structures are grouped according to embryonic development of the brain, as presented in the preceding section. This has not always been the case; terms like “limbic system” remain in use, sometimes leading to confusion. The above figure recalls the developmental parts of the brain.

12.5.3. Neurogenesis

Let us look particularly at development of the neural circuits in the neocortex. This proceeds through a number of steps.

Formation of the brain’s neurons and glia takes place in the tissue of the telencephalon, specifically, in the vesicle walls. Early in its development, the vesicle wall consists of two layers; the ***ventricular zone*** on the inside and the ***marginal zone*** towards the protecting pia. Neural stem cells in the ventricular zone proliferate by splitting via mitosis into two cells. At first, both daughter cells remain in the ventricular zone, populating the zone with neural stem cells. As the population goes up, the daughter cells from horizontal cleavage which are more distant from the ventricular surface migrate upwards to populate the cortex. In this way, the neurons and glia of the cortex are formed from ***neural stem cells***. In humans, most of this cell duplication occurs between the fifth week and the fifth month of pregnancy.

75 https://commons.wikimedia.org/wiki/File:EmbryonicBrain.svg.

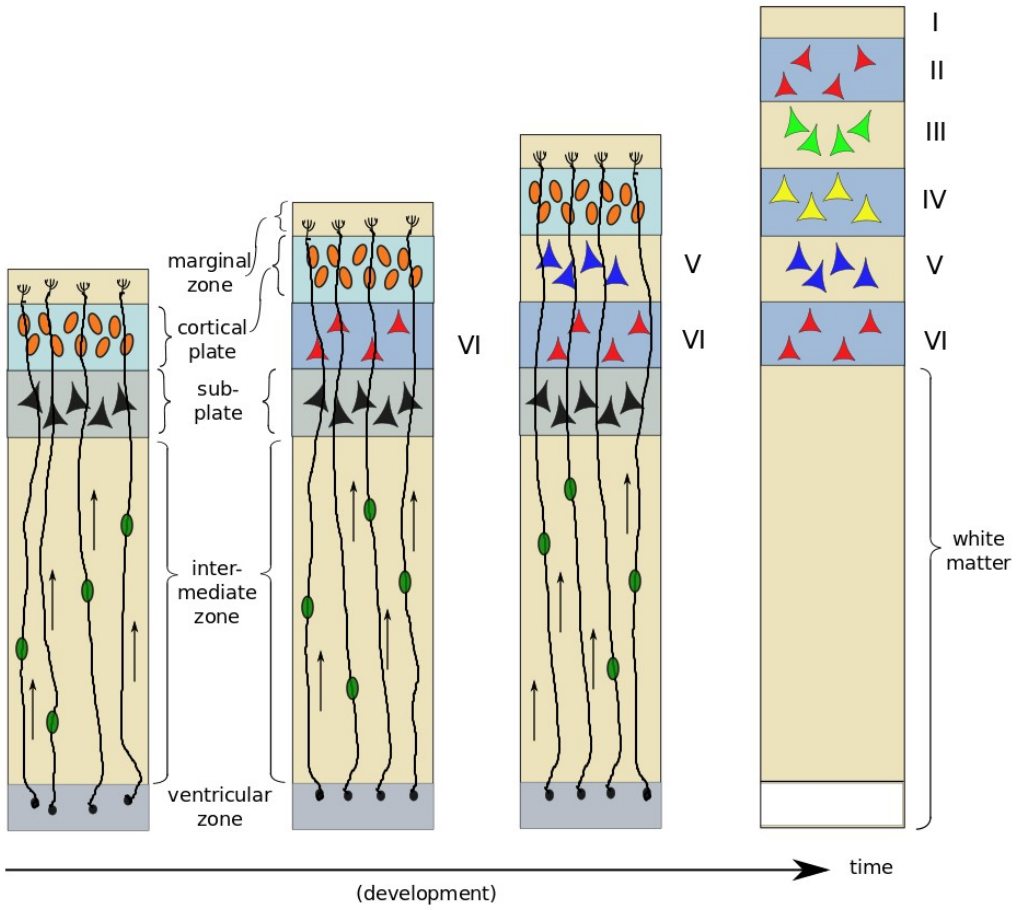


Figure 12.13: Neurogenesis and development of six layers of the striate cortex, by author, after Bear et al.

As a more complex example, consider the six-layer striate cortex.[76] First, radial glial cells extend processes toward the marginal zone; these will serve as "tracks" which migrating cells can follow. The young neurons, or ***neuroblasts***, resemble ordinary cells, and do not yet possess neurites. About two thirds of them follow the radial glial cells upward towards the outer surface of the brain. The first to migrate form a subplate and begin to differentiate into neurons. The next neuroblasts pass through the subplate and arrive in the cortical plate where they start to differentiate in turn. In the case of the striate cortex, they will form layer VI[77], the innermost layer. The next neuroblasts pass by the Layer VI and start to form Layer V. This continues, with one layer being formed after another until all six cortical layers have been formed – in reverse order, or "inside-out". After all six layers are formed, the radial glial cells withdraw the radial processes and the subplate disappears.

On arrival in their respective layers, the neuroblasts differentiate into pyramidal cells first. Afterwards, differentiation of glial cells takes place – first astrocytes and then oligodendrocytes. It has been found that neuroblasts already know what type of neuron they will become before arriving in their appropriate layer. A protein excreted in the marginal zone serves to attract pyramidal-cell dendrites but repel their axons, making them grow perpendicular to the surface and span several layers of cortex.

This laminar structuring of the cortex in horizontal layers formed by radial motion of neuroblasts explains the concept beloved of many neuroscientists of structures called ***cortical columns*** or ***minicolumns***. This idea is based on the finding that discrete surface areas of cortex seem to communicate much more locally, using a leap-frog style of communication to contact more distant

76 Also known as V1, the primary visual cortex, in the occipital lobe.

77 That's a Roman numeral "6", not "Vee one".

areas.[78] Each such surface area is supposed to correspond to a column of cortical layers beneath it. Related to this is the concept that the cortex has pretty much the same ***cytoarchitecture*** everywhere, explaining its plasticity, wherein an area no longer needed for one function can be recruited for another. However, the utility of this concept has been much questioned in recent years, so its fate is not yet clear.[79]

The other third of the neuroblasts, rather than migrating strictly outwards along the radial glial guides, move sideways also.

Most of the input from many parts of the body to the brain comes through the thalamus, which acts as dispatcher, so there are many thalamic inputs to the cortex. It seems that it is the subplate which attracts thalamic neurons to appropriate layers of cortex and thereby establishes which type of sensory input will be handled by that part of the cortex.[80]

12.5.4. Synapse formation and wiring ("la connectique"[81])

Growing neurites advance as the ***growth cone*** at the tip of each one extends ***filopodia*** to drag it along an extracellular matrix of fibrous proteins. During prenatal development, the nervous system is still small and so distances for axons to travel are relatively short. The axons tend to grow in groups of neurites stuck together, each group dragged along step-by-step by one axon called the ***pioneer axon***. The growth cone is attracted or repelled by various chemical substances already released during embryonic development. The concentration gradients of such chemicals guide the axons to their destinations. Attractive ***chemoattractants*** such as the protein ***netrin*** can work in cooperation with ***chemorepellants*** such as ***slit*** to effectively channel the axon along a path. Further detail on connections is furnished by molecular surface markers on target cells; these markers are recognized by complementary markers on growing axons (***chemoaffinity hypothesis***).

This method of connecting neurons is as remarkable as it is necessary. There are not enough coding genes in the human genome to specify all the connections of the 10 billion cells in our brains. What is specified are the functions – chemicals, markers and growth factors – which lead to such formation and connections.

In muscles, when the growth cone finally reaches its target, a neuromuscular junction, a synapse is formed as follows. Both the growth cone and the receptor secrete a proteins which by a sequence of steps do two things. They set up the postsynaptic terminal by attracting ACh receptors (in the case of the NMJ) to the area. At the same time, they secrete Ca^{2+} which acts on the presynaptic terminal in two ways, causing it to emit neurotransmitters and inducing modifications so that it takes on the form of a presynaptic terminal.

In the CNS, similar processes occur, but the steps are taken in a different order and different molecules are involved. Dendritic filopodia constantly reach out and around. When one comes into contact with a passing axon, presynaptic and postsynaptic terminals are installed and a synapse is formed.

Growing in this way, the nervous system comes to contain far too many neurons and, especially, connections. Neurons depend on limited amounts of substances called ***neurotrophic factors,*** which are furnished by target cells. It seems that cells are pre-programmed to commit apoptosis unless they are prevented from doing so by neurotrophins. Since there are not enough such resources available

78 Rather like the Internet's Domain Name System.

79 See for instance "A brief biography of the cortical column", https://evoneuro.org/2014/01/07/a-brief-biography-of-the-cortical-column/comment-page-1/#comment-1594, or "The minicolumn hypothesis in neuroscience", http://brain.oxfordjournals.org/content/125/5/935.

80 See Bear, 697. This process and what it has to do with the non-radially migrating neurons is not clear to me.

81 I couldn't help using the french term here, as it is so simple.

to maintain them all, pruning takes place, as some cells are left to do themselves in. Some neuroscientists see this as an evolutionary struggle for survival among neurons. Up through adolescence, axonal connections are rearranged, synapses used more develop and those used less disappear. In fact, the ***synaptic capacity***, the number of synapses of one neuron, of the striate cortex in adults is about 33% lower than that in infants.[82] This is one form of neuronal plasticity.

The strengthening of synapses will be considered in a later paragraph on learning and memory.

12.6. The forebrain

The forebrain is composed of the telencephalon and the diencephalon. It handles everything which makes us "us" – or at least gives us that impression – including perceptions, consciousness, cognition and voluntary action.

12.6.1. The telencephalon

The telencephalon develops into the ***cerebrum***, the largest part of the human brain, which consists of the cerebral cortex and several elements below it, especially the hippocampus, the basal ganglia (or, more recently, basal nuclei[83]) and the olfactory bulb.

The cerebral cortex

The ***cerebral cortex*** is essential for all sorts of processing of sense data and motor control. It is where the reasoning and cognition specific to humans (and, to a lesser degree, some other animals) takes place. It is the seat of planning and language, volitional behavior and conscious perceptions, thinking and memory. It is the command center where input sensory information is translated into output motor control. In evolutionary terms, it is the most recently developed part of our brains and has taken over or added to function of older structures. Over the last two million years, human brain size has almost tripled, with the greatest relative increase in the frontal cortex.[84]

There are three types of cortex in mammals.

- Inside (medial to) the lateral ventrical on each side is a thin but extraordinarily important layer called the ***hippocampus***, about which more very soon.
- A second type is the ***olfactory cortex***, connected to the olfactory bulb.
- Outside the lateral ventricle and above above the olfactory cortex is the ***neocortex***.

The structure of cerebral cortex differs from that of other brain components. In all vertebrate animals, it possesses a ***cytoarchitecture*** characterized by certain common elements.

1. The cortex is structured in layers parallel to the surface, e.g., six such layers in the striate cortex.
2. The outer layer against the pia mater, referred to as layer I or the molecular layer, contains no neurons.
3. At least one layer contains pyramidal cells with long dendrites, ***apical*** dendrites, which reach up to layer I.

This unique and fairly uniform structure (sometimes termed "canonical") allows for great plasticity in

82 Bear et al say this the other way around: "...the synaptic capacity of immature neurons exceeds that of adult cells by about 50%."

83 Since current standards consider ganglia to be outside the CNS and nuclei inside, otherwise, they are the same.

84 O'Shea, 61.

functioning. Its layered structure consists of ***gray matter*** (neuron cells, dendrites and synapses) on the outside (distally) and ***white matter*** (axons) beneath, although the difference in colors is less pronounced than those terms may imply. The cortex is divided into two lateral ***hemispheres*** joined by a bundle of axonal connections, the ***corpus callosum***, which contains on the order of a million axons, half originating on ei side.

Usually, the left hemisphere handles sensory input from and motor output to the right side of the body and vice versa. The left hemisphere handles more of language and detailed analysis than the right. The right side handles more of visual pattern recognition and overall perception, and seems to be important for the appreciation of music. But the brain is quite plastic (capable of changing) and every brain is different, so any claims to distinctions between the function of left and right brains must be considered as falling in the realm of myth.

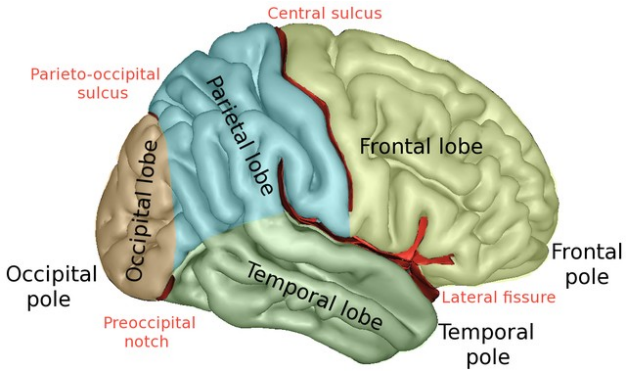


Figure 12.14: The brain lobes, by Sebastian923 via Wikimedia Commons[85]

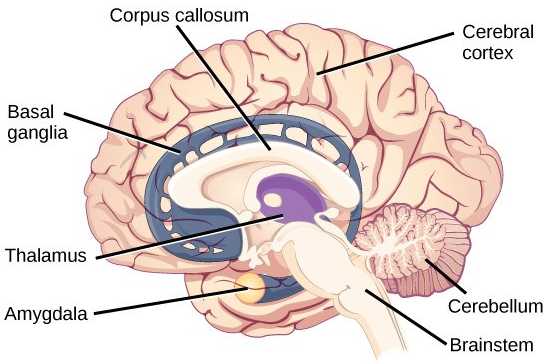


Figure 12.15: Some important brain structures, from Openstax Biology[86]

The cortex consists of five lobes partially separated by the sulci and notches. Functions are distributed among the different lobes as follows.

- The ***frontal lobe***, which is located anterior to the ***central sulcus*** and above the lateral fissure, is important for movement, as it includes the ***primary motor cortex***, just anterior to the sulcus. Perhaps more important, the frontal lobe is the site for planning which takes into account goals and environment. It is also part of the neural circuitry for language and working memory. The activity of this lobe goes from more abstract to more specific (motor) from front to back – from abstract planning to organization of movements to muscle control. The frontal lobe includes a motor map (explained later).
- The ***parietal lobe***, posterior to the central sulcus and above the lateral fissures, receives skin data – touch and pressure – which are mapped here. It also assembles information from other senses, like space around the body and its position and state of movement (***proprioception***), and decides where to direct attention.
- The ***temporal lobes***, on the sides below the lateral sulci, handle auditory processing and visual interpretation. They are also the site of pattern recognition and are essential to language comprehension and speech.
- The ***occipital lobe***, at the back, contains the ***primary visual cortex***, consisting of the visual areas (V1, V2, ...) which analyze aspects of sight, such as color, depth and motion. There is a

85 https://en.wikipedia.org/wiki/File:LobesCaptsLateral.png.

86 https://cnx.org/contents/JOhgnBan@4/The-Central-Nervous-System

retinotopic map on V1 (explained later).

Some parts assure more specific functions:

- The ***lateral prefrontal cortex*** has connections to the rest of the neocortex, the thalamus and the hippocampus. It is the site of short-term memory such as working memory so necessary to understanding the "remembered present"[87], the present and recent past. So it is essential to rationality and planning. Events from short-term memory may be transferred to long-term memory via the hippocampus during REM (rapid eye movement) sleep.
- The ***cingulate cortex*** is an evolutionarily older cortex below the neocortex and is part of the ***mesocortex***. It connects the limbic system with the neocortex. Its forward (ventral) part, the ***anterior cingulate cortex***, which contains the ***anterior cingulate gyrus***, is important in control by the neocortex, telling it when things are not going according to plan. In a computing model of the brain, it would be the scheduler.
- The ***primary motor cortex*** controls voluntary movements by means of axons which run down the spinal column and connect to motor neurons at the neuromuscular junction, as we have seen in a preceding chapter.

Sub-cortical structures

These structures lie below the cortex.

1. The ***hippocampus*** receives input from sensory areas and from the rest of the neocortex and, along with other structures deep within the temporal lobes, such as the rhinal cortex, is *essential* for the formation of declarative or spatial memories.[88] It must therefore have a role in the conversion of short-term memory in the prefrontal cortex to long-term memory.[89]

- The ***amygdala*** has a function similar to that of the hippocampus but concerns events of high emotional content, such as moments of fear. Such memory provides for fast, low-resolution, autonomic responses to recognized stimuli, such as odors or the need for flight from dangerous situations. The amygdala works with the ***orbitofrontal cortex*** (***OFC***) to assess risks and rewards and to choose appropriate behavior and remember it. These memories are our ***emotions*** and may give rise to what we call ***intuition***. Although the amygdala and hippocampus perform similar functions, they have different inputs and outputs.
- The ***basal nuclei*** (formerly called ***basal ganglia***) are hidden deep under the cortex, basal meaning deep within the brain. They are important in planning and executing motor movements initiated by the neocortex. They consist of the ***caudate***, ***putamen***, ***globus palladus***, ***substantia nigra*** and ***subthalamic nucleu***s. The caudate and putamen together constitute the ***striatum***.

12.6.2. The diencephalon

The diencephalon lies beneath the neocortex and consists of the thalamus and hypothalamus and parts of the so-called limbic system.

- The ***thalamus*** is an extremely important double structure which is the gateway for sense data (except olfactory) as well as signals from the rest of the nervous system; it relays the information to appropriate areas of the neocortex.

87 Gerald Edelman's wonderful term.

88 London cabbies who must learn the streets of the city have greatly enlarged hippocampi. O'Shea, 90.

89 Amthor, 275 claims that by projecting the connections it receives back to the neocortex, it activates the same regions which were originally activated by the senses and so forms a mental representation of the sensory perception. This amounts to a replay of the original event. But this "rewrite" is not mentioned by Bear et al. or by O'Shea.

- The **hypothalamus** has important control over the autonomic nervous system depending on input it receives from other brain areas. As has been discussed in section Error: Reference source not found, it is the brain's gateway to the endocrine system via the pituitary gland, the posterior pituitary being an extension of the hypothalamus. Its initiation or inhibition of endocrine hormone release allows it to assure *homeostasis* by producing hormones which regulate essential functions (temperature, blood pressure, hunger, thirst, circadian rhythm, etc.).

The ***limbic system*** is an evolutionarily old set of structures which existed before mammals. The term limbic system is historical and does not refer to an integrated structure, so it is often denigrated. It is subcortical (lies beneath the cortex) and is considered to be constituted by a number of structures, including the thalamus, hypothalamus, cingulate gyrus, basal ganglia, hippocampus and amygdala, all of which we discuss elsewhere:[90]

12.7. The midbrain

Nuclei (groups of cell bodies) in the mid- and hindbrain play a role in essential, non-cognitive functions such as respiration, blood circulation and level of consciousness. They are phylogenetically very old and exist in all vertebrates.

The midbrain, or ***mesencephalon***, includes the following structures.

- The ***substantia nigra*** (also considered one of the basal ganglia) is involved in the initiation and maintenance of voluntary movements. Damage to it is linked with Parkinson's disease.
- The ***inferior colliculu***s receives audial information and relays it to the thalamus.
- The ***superior colliculus*** receives visual information from the eye and, in turn, controls eye movements (***saccades***). It holds maps of the visual world. The superior and inferior colliculi together form the ***tectum***, the top of the midbrain.
- The ***reticular formation*** runs from the midbrain into the spinal cord. It has a number of different modulatory functions, including control and regulation of the brain's state of arousal and consciousness.[91]
- The ***diffuse modulatory system*** consists of the ***locus coeruleus***, ***raphe nuclei, substantia nigra*** and ***ventral tegmental areas***. These cells perform regulatory functions as each of them sends small amounts of a specific neurotransmitter across wide areas of the brain or spinal cord. They can be thought of as a kind of volume control.[92]

12.8. The hindbrain

The hindbrain, or ***rhombencephalon***, supports vital processes.

- The ***medulla*** is a communication path for axons between the brain and spinal cord and is the place where axons to or from the rest of the body change sides (***decussation***). It controls automatic functions such as breathing, heartbeat, hearing, touch, taste and swallowing.
- The ***pons*** is anterior to the medulla and has a role in visceral functions and facial expressions. It contains centers like the ***vestibular nuclei***, which receive information about orientation of the body relative to gravity and acceleration, so it is partly responsible for balance. As its name implies, it forms a bridge between the cerebral cortex and the cerebellum.

90 The term "limbic system" is historical and its members are not all in the same embryonic structure. O'Shea, 56, points out that *limbus* in Latin is "rim" and these structures are around the rim of the corpus callosum.

91 Information up to here on the midbrain, as well as on the hindbrain, is based mainly on O'Shea, 53-57.

92 Bear et al., 498.

- The ***cerebellum*** (“little brain”) is the most complicated part of the hindbrain. It consists of two lobes at the back of the brainstem. In terms of size, it is second after the cerebral hemispheres. It receives input about the body from the spinal column and about goals of movements from the cortex and coordinates the two. It also memorizes information needed for complex motor skills. Unlike the cerebral cortex, each side controls *its own* side of the body. Without the cerebellum to modulate and coordinate motor behavior, you would not be able to ride a bicycle – or walk. The cerebellum is the oldest part of the brain from an evolutionary point of view and is necessary to all animals, at least to vertebrates.

12.9. The spinal cord

The ***spinal cord*** manages basic life-critical functions such as reflexes, breathing or heart rate; its actions are usually unconscious.

As already explained, the spinal cord is segmented, each segment having two pairs of ‘roots’ connecting the spinal cord to other parts of the body.

- The ***ventral roots*** are outgoing (efferent) motor-neuron axons, clustered in functionally related groups. Their cell bodies are within the spinal cord.
- The ***dorsal roots*** are the incoming (afferent) sensory-neuron axons. Their cell bodies are in dorsal root ganglia, near the spinal cord.

Interneurons may connect the incoming and outgoing circuits so as to allow rapid reflex reactions, like the knee jerk. They also relay commands coming from the brain.

12.10. Input from the sensory systems

Let us look at examples of brain circuits by regarding the different sense organs. But first, a word about maps.

12.10.1. Cortical maps

In many cases, sensory data arriving in the cortex do so in such a way as to define a ***cortical map.*** In general, adjacent sensory areas are also adjacent to each other on the map, although the map may be so grossly distorted that this is not always the case. ***Somatotopy*** is the mapping of points on the surface of the body onto a brain structure. It is like a map of the Earth projected onto a flat surface, but even more distorted because the size of the cortical area attributed to a given area of skin surface is proportional to its importance rather than to its original size. In a somatotopic map, the area of cortex corresponding to the lips is huge in comparison to that of the trunk or hip, as is obvious in the following figure.

Since adjacent areas of the map do not always correspond to adjacent organs, leakage or “cross-talk” between the areas may lead to confusion of senses, as in the case of ***synesthesia***, in which a person may see numbers or hear musical tones as possessing colors.[93]

93 Could they also be the basis of metaphor?

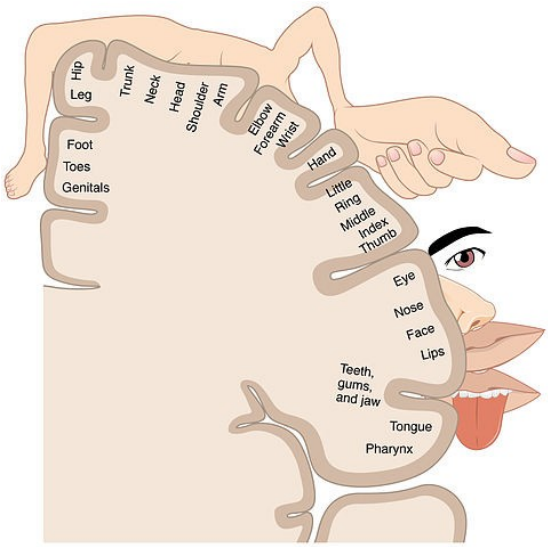


Figure 12.16: Somatotopic map, from Openstax College[94]

Similarly, the retina of the eye and the cochlea of the ear, sensitive to frequencies of, respectively, light and sound, map via ***retinotopy*** and ***tonotopy***. There are multiple somatotopic and retinotopic maps in the brain.

There are differences between species. The vibrissae of cats and rodents receive a much larger share of the map than do our upper-lip whiskers.

12.10.2. Vision

That vision is by far our most important sense is clear from the huge part of the brain dedicated to the processing of visual data: Almost half of the neocortex is taken up with visual processing.

Vision in the eye

It starts when light of wavelengths between about 390 nm and 700 nm (ultraviolet to infrared) passes through the cornea, which does most of the focusing of the light; then through the iris and the lens, which does some more focusing; through the vitreous humor and onto the photoreceptors of the retina, at the back of the eye.

Each retina is actually part of the brain, growing out of the diencephalon during embryonic development. The visual receptors in retinas are photoreceptors, like metabotropic ion channels but sensitive to light. Light energy causes a change in a molecule in the receptors and this brings about a reduction in the number of depolarizing ion channels. There are two types of photoreceptors:

- ***Cones*** are receptive to colors, some to red, some to blue and some to green (approximately). But they are much less sensitive to light than are rods. They are more concentrated in the center of the retina around the ***fovea***.
- ***Rods*** are more sensitive to light (1000 times more than the cones), but do not distinguish colors. They are more populous around the periphery of the retina.

94 Via Wikimedia Commons, https://commons.wikimedia.org/wiki/File:1421_Sensory_Homunculus.jpg, Funny, there's no illustration for the genitals. Maybe they couldn't decide on a sex.

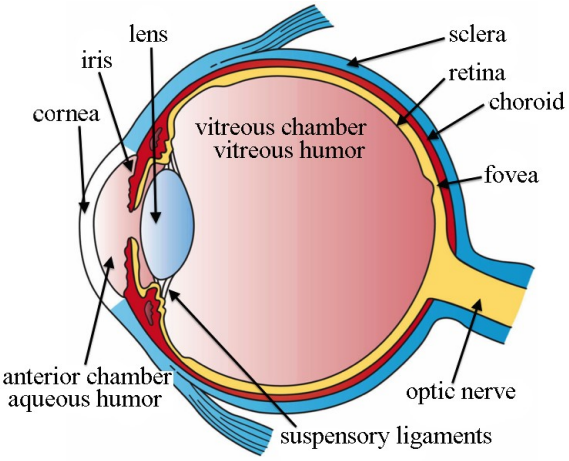


Figure 12.17: Eye structure, by Holly Fischer via Wikimedia Commons

Each retinal photoreceptor, rod or cone, is composed of an outer segment (farthest from the lens, in other words, at the back), an inner segment, a cell body and a synaptic terminal, which connects to bipolar and horizontal cells. Light reception takes place in a column of disks which are stacked parallel to each other in the outer segment.

A photoreceptor cell in total darkness is at a membrane potential of about -30 mV, due to the existence in the cell membrane of open Na^+ channels. These channels in effect allow a current, called the ***dark current***, which works against the Na-K pump and partially depolarizes the cell. In this state, it continuously releases the neurotransmitter glutamate.

When light impinges on the photoreceptors, a pigment within the cell (***rhodopsin***, in rods, three similar but different types of ***opsins***, in cones) momentarily changes its form and color. An opsin is like a metabotropic channel in the disk membrane, but its receptor is blocked by an agonist[95] called ***retinal***, which is a derivative of vitamin A.[96] When EM radiation (light) is absorbed by the retinal, it changes the conformation (shape) of some of the bonds from cis to trans, and this changes its shape and color (so the process is called ***bleaching***). This triggers the series of processes leading to closing of Na^+ channels and hyperpolarization of the cell. The opsin stimulates a G protein to activate an enzyme which in turn breaks down molecules of the second messenger cGMP (cyclic guanosine monophosphate). The reduced concentration of cGMP causes Na^+ channels to close. Less input of Na^+ means that the cell's membrane potential becomes more negative, which is to say that the cell *hyperpolarizes* and this causes less glutamate to be released.

So photoreceptors work backwards to what one might suppose. It is the darkness of a passing shadow, not a flash of light, which causes the receptor to depolarize and release more glutamate.

In the human eye, only the ganglia (and a few ***amacrine cells***) form action potentials. The others communicate by ***graded potentials*** – changes in membrane potentials below the threshold for initiation of an action potential.[97]

The number of receptors on the retina, on the order of 100 million, is far too great and sends information too fast for it all to be sent to the brain, especially as there are only around a million axons leading to the brain. So, in between light reception by the photoreceptors and output from ganglion cells to the brain, some ***information*** processing takes place within the retina.[98]

95 A substance which binds to a receptor.

96 Hence the importance of vitamin A for vision.

97 Bear et al., 298-299.

98 This can be likened to the Control Data Corporation supercomputers of the 70s (which I knew well), which had one central processor for mathematical and logical calculation, and a number (on the order of 10) of smaller, independent so-called peripheral processor units which handled input-output and storage devices.

As a result, each optic ganglion reports an average of the signals from the receptors which feed it, its ***receptive field***. This process occurs as the output from the photoreceptors passes through two other types of cells (horizontal and bipolar) before they reach the output cells, the ganglia. Quite ingeniously, these cells enable receptors in the center of the ganglion's receptive field to signal light intensity with the opposite sign to that of receptors around the center. So the net result to the ganglion is the difference in the overall signals from the center and the surrounding area. This may be difference in intensity or in color. No difference between the center and surrounding areas means no action potential generated by the ganglia and a subsequent reduction in neural traffic. Such a receptive field is an *antagonistic* ***center-surround receptive field***. Such ***lateral inhibition***, reduction of a neuron's signal by those of its neighbors, is also characteristic of information processing in other sensory pathways.

In yet more detail, cells in the retina are arranged in layers. Output from the photoreceptors passes through ***bipolar cells*** (so called because they have two processes), which lead the signal towards the ganglia, and ***horizontal cells***, which transmit them laterally.

There are two types of ***bipolar cells***:

- OFF bipolar cells are glutamate-gated ion channels which depolarize on stimulation by glutamate, i.e., when light is OFF.
- ON bipolar cells have G protein-coupled receptors and are hyperpolarized by glutamate, i.e., they are depolarized by less glutamate due to light ON.

Whatever the curious logic behind these names, the important point is that there are two types of bipolar cells with opposite reactions to a glutamate.

Remember: Only photoreceptor cells are light-sensitive and only retinal ganglion cells (***RGC***s) send signals to the brain by action potentials. The bipolar, horizontal and amacrine cells are components of the "firmware" which "computes" what gets sent from photoreceptors to RGCs.

Each bipolar cell is connected to photoreceptors in two ways:

- The center of an RGC's receptive field is connected directly to a group of receptors by bipolar cells. The number of receptors per receptive field varies from one, in the middle of the fovea, to thousands on the periphery, with corresponding inverse variations in optical ***resolution***;
- The surrounding area (called the receptive field surround) of the RGC's receptive field is connected indirectly through the intermediary of horizontal cells which invert the effect of light from the surrounding area, giving it opposite polarity to that of the center.

So the RGC receives a total signal which is the amount of light in the middle of its receptive field minus an adjusted amount of light in the surrounding area.

Figure 12.18 shows how one horizontal cell can link two receptors. The resulting algebraic sum of the two fields gives the difference of the polarizations and may be positive (depolarized) or negative (hyperpolarized).

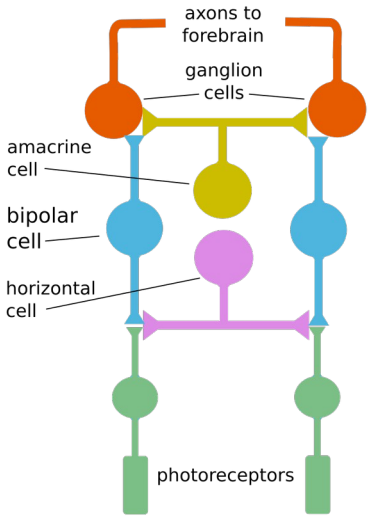


Figure 12.18: Basic retinal cell processing, by author after Bear

But there is more. At the next level, the ***inner plexiform layer***, there are ***amacrine cells*** which have multiple functions. Since they do not seem to participate in the center-surround process, we will not consider them further.

The result of retinal information processing is that ganglion cells have center-surround receptive fields, functioning as follows:

- An ON-center ganglion emits an action potential when light strikes only the middle of its receptive field.
- An OFF-center ganglion emits an action potential only when light is off in the center of its receptive field.

Only a difference in illumination over the center-surround receptive field will generate a ganglial action potential. This is an effective way of limiting the traffic through the optic nerves.

Note the energy changes. EM energy (light) is converted into a change in membrane potential in the photoreceptors. They in turn convert this into chemical energy in the form of the neurotransmitter glutamate. This stimulates further changes in the membrane potential of bipolar and horizontal cells which eventually pass the information on to ganglia which fire action potentials.[99] The energy undergoes a number of conversions, light to chemical to electrical to chemical... Of course, each conversion is accompanied by an increase in global entropy.

Center-surround cells also provide a way to detect edges, as the center and surrounding areas do not quite cancel out in the case of all light or all dark, but have different results in these two cases. Consider a dark edge moving in over an OFF-center GCR field.

1) Initially, when entirely lighted, the GCR may have a weak response.
2) As a dark edge moves over it and shades only one side of the surround field, the response diminishes to essentially nothing.
3) As the dark covers the center also, the response becomes quite strong.
4) When the dark entirely covers the field, its response will be weaker although a bit stronger than when all lighted.

More mathematically,

response (3) > response (4) > response (1) > response (2)

99 I cannot find how bipolar cells influence ganglia, except for a reference to “graded potentials”.

So movement of an edge across a group of retinal receptive fields gives rise to a characteristic sequence of action potentials. It also may give rise to the illusion of a gray square's appearing lighter against a dark background, but darker against a light one.

A similar mechanism is used in some color-detection ganglion cells. For instance, a color-opponent cell of type R^+G^- has a red-sensitive center field and a green sensitive surround field, so that green around red inhibits signaling of the red. So white light, which contains all wavelengths, would cause the two fields to cancel out.[100]

Adaptation to sudden light or dark requires resetting of the "standard" intensity to match current conditions. Among its several components is the relatively minor one of the opening and closing of the pupil to allow more or less light to come in. More important – and more amazing – is the re-arrangement of the circuits of bipolar and horizontal cells to pass information from more rods to the ganglia, in the case of dark adaptation. Also, more fresh, unbleached rhodopsin must be generated. (Normally, rhodopsin is regenerated in about 30 minutes.) The opposite processes take place in the case of adaptation to sudden light.

Vision in the brain

Each ganglion signals the difference between light intensity in its receptive field and the average background as defined during adaptation. This information is sent primarily to the thalamus.

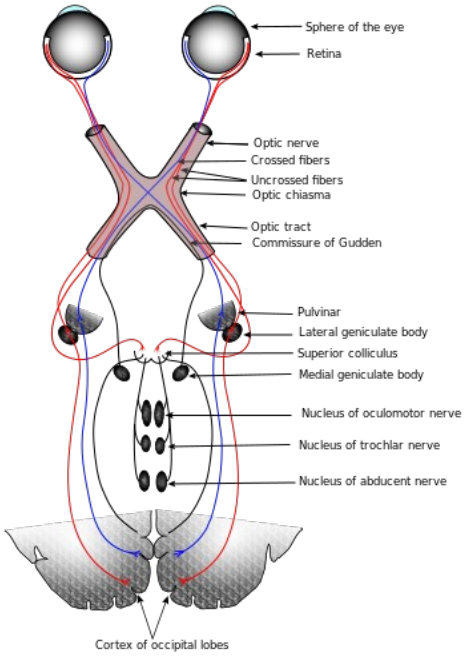


Figure 12.19: Connections of the human visual system, after Gray's Anatomy via Wikimedia Commons[101]

The part of the thalamus receiving vision information is the ***dorsal lateral geniculate nucleus***, or ***dLGN*** or, more simply, the ***LGN***. Optic nerves (bundles of axons) carry information from the left side of each eye to the right side of the LGN, and vice versa, crossing over at a point called the ***optic chiasma***, with approximately 60% of axons crossing over due to the overlapping of the left and right visual fields. So one entire side of the visual field, rather than one entire eye, is processed by the opposite side of the brain. The nerves carrying visual info from the chiasma to the LGN are called the ***optic tracts***, to distinguish them from the ***optic nerves*** between the eye and the chiasma, and terminate at the LGN.

100 I find the functioning of retinal cells is as *genial* as some of the other marvels of the scientific world, like the electron transport chain.

101 https://commons.wikimedia.org/wiki/File:Gray722-svg.svg

Amazingly, after all this mixing of signals in the same optic tract, all gets sorted out again in the LGN. The thalamus then transmits the information to the primary visual cortex,***Visual Area 1*** (***V1***), in the occipital lobe.

Visual information in the cortex is organized such that adjacent regions in the visual scene are also in adjacent neurons in the cortex - another map. Information may be handled in a hierarchical fashion. For instance, some neurons are sensitive only to edges with a specific orientation and in a specific area of the visual field. Others may be sensitive to that orientation in any area. Eventually, information may travel to V2 and V3 and others, where different features are analyzed: movement direction, depth, orientation, form, translation, parallax, colors, faces and more.

Information from the optic tract goes not only to the thalamus but to over a dozen other areas. Among these are zones like the ***superior collicus*** for controlling eye movements, or ***saccades***, retinal slip and visual tracking (keeping your eyes on a moving target); the hypothalamus for control of ***circadian*** (night and day) rhythms; and the pretectum of the midbrain for contraction of the pupils (both together).

Visual information is thus deconstructed into different aspects which are analyzed in different parts of the brain. They are then reconstructed, but the existence of illusions makes it clear that the reconstruction is somewhat approximate. The brain supplies from memory whatever additional data is needed to generate a coherent "image" of the visual world. Something similar is true of the other sensory systems too. Together, they generate hypotheses and then proceed to abduct[102] the best result. Perception is creative.

Saccades are necessitated by the small area of the fovea. Data sent to the brain is used to calculate where to look next and this information is returned to the eye in yet another feedback loop. The way this works is quite fascinating – and simple. Input visual data is mapped onto the surface of the cortex. A layer just below it contains a motor map arranged in such a way that excitement of a point on the visual map triggers the adjacent point on the motor map to generate a saccadic movement to the appropriate point.[103]

Similarly, as pointed out in Chapter 8, special muscle fibers called muscle spindles are stretch receptors which can control increments in muscular strength when, for instance, holding a glass of water which is being filled, so that its weight slowly increases. The whole process takes place without conscious monitoring. Regulation of the biceps and triceps in this case results from synapses of sensory axons with motor neurons in the spinal column. This is one example of many such automatic control mechanisms which operate through the spinal column.

Evolutionary considerations

Considering the existence of the photosynthetic pigment rhodopsin across space and time reveals aspects of the evolution of vision.

As we have seen in chapter 7, formation of an eye at a particular place in all animals depends on the homeobox gene ***Pax6***. Remember that Pax6 codes for a transcription factor, not for a gene. Pax6 also influences brain formation. Not only does Pax6 occur in almost all vertebrates and invertebrates, but so do opsins. What is more, the human retinal ganglion contains a kind of opsin called melanopsin, which has a role in circadian rhythms. But melanopsin is characteristic of invertebrate photocells. All these observations suggest a common source for photocells across the vertebrate-invertebrate world.

It is generally accepted that photocells in vertebrates and invertebrates evolved from a common

102 "Abduct" is used here as somewhat the opposite of induct and means to choose the best possible explanation from the data available plus whatever prior information (memories) is to hand. Carroll (2016), 41.

103 O'Shea, 78.

ancestor.[104] Somewhere along the line, this cell was duplicated, one type to become eyes, the other, circadian detectors. The eye was originally an area of light-sensitive cells on the surface of the skin. Then epithelial folding moved the cells into a cavity, lenses formed, and so forth, on up to animal eyes today.

Here's the punch line: Rhodopsin is found in chloroplasts, the organelles in plant cells which convert energy from sunlight into ATP. So the original photosensitive organism was also the ancestor of chloroplasts and was very likely our old pal *cyanobacteria*!

Figure 12.20: Erbernochile erbeni (a trilobite) eye detail, Large compound eye with "eye-shade". By Moussa Direct Ltd, via Wikimedia Commons.[105]

The first animals to have image-forming lenses (and there were a lot of them, lenses and animals) were probably trilobites, whose eyes came to be composed of multiple oriented calcite lenses. These eyes date from 540 Mya, just after the start of the "Cambrian explosion". With certain assumptions, it is possible to show that eyes could develop quickly enough that, in tandem with size increase due to enhanced oxygen content in the air, predators developed. So the eye may have been the match which lighted the Cambrian explosion.[106]

12.10.3. Hearing

Hearing depends on ionotropic mechanoreceptors based on selectively depolarizing ion channels. First, sound energy is reflected and directed by the earlobe (***pinna***) , which can detect some vertical direction and modulates the frequency some as a function thereof. Then the energy passes through the ***auditory canal*** of the so-called ***outer ear***, whose sensitivity is subject to resonance at the mid-tones we use to distinguish sounds. At the end of the canal, the sound wave hits the ***eardrum*** (***tympanic membrane***). This membrane is connected to the trio of tiny bones – the ***hammer*** (***malleus***), ***anvil*** (***incus***) and ***stirrup*** (***stapes***) – which use physical leverage to bring about slighter but stronger movement where the stirrup presses against the entry membrane to the cochlea, the ***oval window***. The ***cochlea*** is rather like a nautilus shell, larger at the entry and spiraling somewhat to a smaller end. Its walls are lined with fine hairs which have finer hairs upon them, called ***cilia***. As the cilia are moved by the sound energy, they stretch the hair-cell membrane, causing the stretch-sensitive mechanoreceptors in the membranes to depolarize. The resulting action potential sends information about the frequency and amplitude of the sound along the auditory nerve. The wider entrance of the cochlea detects higher frequencies, the small end, lower, so that frequency is a function of position in the cochlea.

104 Lane (2010), 199.

105 https://commons.wikimedia.org/wiki/File:Erbenochile_eye.JPG

106 Lane (2010), 185.

[KANDEL, 12: Wernicke's model of hearing]

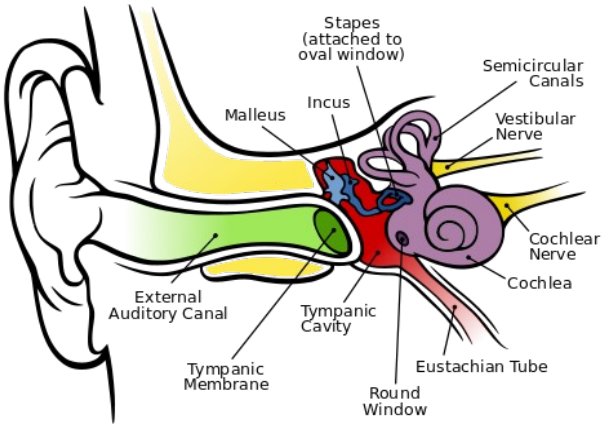


Figure 12.21: The human ear, by Chitta L. Brockmann, via Wikimedia Commons[107]

Also visible in Figure 12.21 are the three ***semicircular canals*** which constitute the ***vestibular system***. They are oriented so that they can detect rotation and angular acceleration of the head about three axes and, so, in three dimensions. Not shown are the utricle and saccule, ***otolith organs*** which detect not only head tilts but the force of gravity. They and the semicircular canals are also lined with cilia and the set of vestibular and auditory cilia on either side of the head is said to constitute a ***vestibular labyrinth***. Nerves from these systems are used by different parts of the brain in conjunction with ocular information and proprioception to detect and maintain the body's orientation. They also contribute to the ***vestibulo-ocular reflex*** (***VOR***), which enables us to keep our eyes on a subject in spite of head movements.

The signals detected by the cilia are sent through other structures and finally arrive in the ***inferior colliculus*** of the thalamus on the opposite side of the brain. The thalamus relays the information on to the primary audio cortex, A1, in the superior temporal lobe, on whose surface location is a function of frequency, rather like the skin (somatosensory) map. It is not completely understood what happens after that. It is known though that two areas on the left side of the brain are important.

- The zone called ***Wernicke's area*** is necessary to the understanding of language.
- Similarly, ***Broca's area*** is necessary for producing speech.

Although these two areas are found on the left side of the brain in most right-handers, the right side also seems to be necessary for the comprehension of prosody (change of tonality and rhythm in speech). So it is logical that the right side appears to play a role in the appreciation of music.

Detection of sound direction, though less good than in the case of vision, is accomplished vertically by the pinna, as already mentioned, and horizontally by the difference in intensity and arrival time of the sound in the two ears. Detection of minute delays in arrival time is accomplished by coincidence detection in the ***medial superior olive*** (***MSO***) in the brainstem. A sound from the left will have more time to move to the right within the brain while the sound goes around the outside and into the right ear. So the neuron stimulated the most will be the one where both signals arrive at the same time, to the right in this example. Note that a distance in space is translated into an interval of time which is then interpreted by neurons at two different places: space → time → space. It is the final spacing on neuronal dimensions which allows the detection of temporal differences on the order of 10 microseconds.[108]

107 https://commons.wikimedia.org/wiki/File:Anatomy_of_the_Human_Ear_en.svg.

108 O'Shea, 80-81.

12.10.4. Touch

Touch, or ***somatosensory*** perception, takes place in ionotropic mechanoreceptors mostly in the ***dermis***, the lower part of the skin. The outer layer, or ***epidermis***, is composed of sloughed-off dead cells from the dermis and constitutes a mechanical protection layer. The receptor cell bodies are in ***dorsal root ganglions***, concentrations of cells just posterior to the spinal cord. Such a cell has no dendrites and only one axon, which bifurcates, the end of one branch being the receptor in the dermis. Whereas most axons are output channels, carrying an action potential to a synapse, the branch from the receptor is actually an input. An action potential from the mechanoreceptor passes up the axon to the bifurcation where it travels out the other axon branch. This branch leads into the spinal column where it connects to interneurons. The interneurons connect locally to motor neurons to control reflexes. Signals pass only through one or more segments of the spinal column without reaching the brain, so we are as yet unaware of the sensation. The interneurons then carry the signal up the longer route via the spinal column to the thalamus on the opposite side of the brain from the receptors. Only then can we be conscious of the sensation, perhaps some time after the movement is initiated.

Four types of mechanoreceptors are sensitive to specific stimuli: constant pressure over a small area; sudden changes in pressure; stretching of the skin; and very rapid changes in pressure, as when you rub your fingers across a coarse surface.

In addition, the dermis contains receptors referred to as ***free nerve endings*** with ion-channel receptors sensitive to temperature, extreme force or other possibly dangerous contacts. There are also receptors in muscles, tendons and ligaments which signal position (***proprioception***) or movement (***kinesthesis***).

The ventral posterior nucleus of the thalamus relays the signal to the ***somatosensory cortex*** (parietal lobe) just behind the central sulcus, where it is localized on a skin map as shown in Figure 12.16. In the map, the signals from a fairly well-defined part of the skin (such as the face or a hand) are found together. Outputs from the map connect to memories of previous touch-associated events. Cross-talk between adjacent areas of the map may lead to confusion as to the source of a stimulus.

12.10.5. Smell (olfaction)

The olfactory bulb in the top of the nose canal contains about 10 million olfactory receptors of about 1,000 types. They are metabotropic receptors on the cilia of the bulb. A smell is detected by many receptors of different types and is distinguished by a superposition of the different results.

Olfaction is the only one of our senses whose receptors do not send information to the brain by way of the thalamus. Instead, they project to several sites in the cortex, including the olfactory cortex, which has direct influence on various brain areas. Information also passes via the olfactory tubercle of the olfactory cortex to the thalamus, which transmits it to the orbitofrontal cortex in order to bring about consciousness of the odor. Other parts of the cortex control unconscious or reactive odor detection and memorization of smells.

The reason the olfactory receptors bypass the thalamus is evolutionary and is probably due to the fact that our ancestors already had a highly developed sense of smell, much like many animals today. So all that was left was to relay the smell to the thalamus in order for it to become conscious.

The receptors also send information to, among others, the amygdala for emotional response (e.g., for spoiled food) and to the hippocampus for memorizing of smells.

12.10.6. Taste

The surface of the tongue has structures called ***papillae***, in which there are four types of receptors, only three of which are taste buds, containing about 10,000 taste cells. Each cell has several receptors

responding to five different basic tastes: sweet, salt, bitter, sour (acid) and umami (meaty). Some are ionotropic, some metabotropic.

Signals pass from the receptors through another structure, the ***nucleus of the solitary tract*** (***NST***) in the brainstem, to the thalamus either as pure basic tastes or mixtures. The thalamus relays it to the cortex for consciousness of the taste. Connections with the amygdala allow recognition of tastes associated with bad experiences in the past and so to be avoided. The NST, which influences the ANS, also receives input which may signal that you have eaten enough of that taste.

We distinguish different tastes far less well than different smells. Taste information is joined with olfactory information in the orbitofrontal cortex to generate ***flavor***. Flavor therefore suffers if, for instance, our olfactory mucus is affected by a head cold.

12.11. Output from the nervous system

We have already seen how afferent axons from sensory receptors enter the spinal column through the dorsal root and motor neurons exit through the ventral root. The afferent and efferent axons are grouped into spinal nerves before separating to go their separate ways. Once outside the spinal column, these axons and nerves are part of the peripheral nervous system, or PNS. We also have seen how efferent axons connect to muscle fibers via the neuromuscular junction (NMJ) to initiate muscle contraction. So not very much is left to add without going into much more detail.

As far as output from the nervous system is concerned, there are two parts:

- the somatic motor system, which controls conscious perception and voluntary motor response, and
- the autonomic nervous system (ANS), which is responsible for involuntary control, such as of the glands, heart and involuntary muscles .

There are three sorts of movement, controlled by different neural circuits:

- involuntary movements which regulate internal functions and homeostasis;
- conscious voluntary movements;;
- reflexive movements, automatic reactions which nevertheless may become conscious.

The third type, ***reflexive movement***, is a fast, protective mechanism, which generally occurs before the brain is informed of the situation. Instead of the sensory neurons' contacting the brain to obtain a command, these signals pass directly to interneurons in the spinal column and from there back out to the muscles, thereby avoiding the delay which would result from contacting the brain to obtain a response. This is of course how the classic knee-jerk reaction works. The interneurons are linked together into networks. The signal may also be passed to the brain to become conscious.

The ***anterior cingulate cortex*** compares plans to how things are really happening in order to correct for errors or trouble due to unforeseen circumstances, including pain or the perception thereof. It also monitors progress towards goals. It is connected to the lateral prefrontal cortex, giving it access to working memory.

We will not look any deeper on the subject of motor control.

12.12. Learning and memory

Memory is stored in the brain by means of neural connections (circuits) and so is based on synaptic weights – relative strengths of synapses. These are not programmed in our genes, if only because there are not nearly enough genes to contain such an immense recipe. Instead, synaptic enhancement is due to correlated activity brought about by chemical substances between the

presynaptic and postsynaptic elements. This method has the advantage of allowing environmental influence on learning.

It hardly needs to be pointed out that memory is essential not just to what we are, but to our very survival. The "present" we inhabit is really a collection of memories, some from the last milliseconds (what we see as "present'), filled out by and compared to memories of similar past experiences. It really is the "remembered present".[109]

12.12.1. Types of learning and memory

For one thing, memory can be short-term, one type of which is ***working memory***, or long-term.

Neuroscientists and, especially, psychologists distinguish several types of long-term memory, which have different functions and are handled and stored differently in the brain.

- ***Explicit*** or ***declarative memory*** is conscious. It starts out as short-term memory in the pre-frontal cortex and may later be stored as long-term memory via the hippocampus. Explicit memory in turn is divided into two parts.
    - ***Semantic memory*** refers to remembered facts.
    - ***Episodic memory*** refers to remembered experiences, events and episodes.

The difference between episodic and semantic memory can be remembered by an example: I know that giraffes spread their front legs in order to reach nutrients on or near the ground. That's semantic memory, of a fact. Such facts are shared, my wife agrees on that, and so tend to be impersonal. They include spatial memories and are necessary for getting along in the world. However, I think I learned that fact about giraffes on a BBC wildlife documentary, whereas my wife thinks we learned about it when we saw giraffes on a safari in Tanzania. That is episodic memory; context has been added. Episodic memories are more personal than semantic ones, and more liable to be false.

- ***Implicit*** or ***procedural memory*** is unconscious. It contains what is necessary for all those procedures we do without thinking, like riding a bike or driving a car, playing a musical instrument or tennis, or simply unscrewing a bottle cap. It is in fact a collection of different systems and depends on the amygdala (emotional responses), the cerebellum (motor control) or the ***striatum***, a part of the "***reward system***" and input to the basal ganglia (procedural memory).

Scientists also study several types of implicit or procedural learning.

- ***Non-associative learning*** describes memory due to a single stimulus. The two types of non-associative memory are:
    - ***Habituation*** is just that, getting used to a mild stimulus (such as background noise) so you stop paying attention to it.
    - ***Sensitization*** is the opposite of habituation and is provoked by a stronger stimulus. It is like "getting burned" once so any heat frightens you unduly afterwards.
- ***Associative learning*** forms associations between two events and also exists in two types.
    - Whereas habituation and sensitization are due to a single stimulus, ***classical conditioning*** is the association of two stimuli, a neutral stimulus (like a bell ringing) with a real or effective one (the smell of food). The effective response is called the ***unconditional stimulus*** (***US***) because it works all the time; the learned one is called the ***conditional stimulus*** (***CS***). Such conditioning is effective only if the CS occurs at the same time as or slightly, but not too much, before the US.

109 Edelman (2006).

- ***Instrumental conditioning*** is associating a stimulus or behavior with a reward or result. For instance, pushing a lever gives food.

12.12.2. Simple implicit learning in invertebrates

Several mechanisms for learning have been identified, all based on the basic fact of learning and memory, which is this:

> *Neural circuits, the basis of what goes on in the brain such as learning or plasticity, are set up by modification of synaptic strengths.*[110]

This synaptic modification depends on *correlated* activity in pre- and postsynaptic terminals. The idea is conveyed by the popular statement, "Neurons that fire together wire together."

Consider some examples which give a good idea of the process – or processes – behind learning. They also illustrate what seem to be some common components of all learning.

12.12.3. Short-term learning in invertebrates

Studies of the giant sea slug, *Aplysia*, have demonstrated mechanisms for implicit learning.[111] A simple stimulus, a puff of air on a part of the animal called a siphon, causes a reflexive retraction of the gill; this is called the ***gill-withdrawal reflex***. After a series of gentle puffs, the animal becomes **habituated** and no longer retracts the gill as much. Molecular study of habituation has found it to be due to the presynaptic terminal, specifically to the production of less Ca^{2+} and therefore reduced release of the neurotransmitter, glutamate, by the synaptic vesicles.[112] Exactly how this happens is not yet known. Nevertheless, the animal has *learned* that the gentle puff is not worth getting excited over. The effect is short-term, it disappears after a while.

When a stronger stimulus, a series of electric shocks, is delivered to the head or tail, the animal retracts the gill quickly upon even a gentle, subsequent puff on the siphon. It has become ***sensitized***, without any simultaneity of the two signals.

In sensitization, the axon of the sensitizing or modulating neuron from the tail makes synapses on the presynaptic axon terminal of the sensory neuron from the siphon at its synapse with the motor neuron to the gill. (So synapses are not always formed between an axon and a dendrite.) The series of tail shocks causes the modulating neuron to release a different neurotransmitter, serotonin, as a first messenger into the synapse between itself and the presynaptic terminal of sensory neuron. The first messenger activates a metabotropic receptor on the sensory axon terminal and this in turn releases a second messenger inside the axon – our old friend cyclic AMP, or cAMP.[113] The cAMP activates an enzyme called ***protein kinase A***, or ***PKA***.

Kinases activate a substrate by phosphorylation, adding a phosphate group to it. PKA itself is composed of two regulatory and two catalytic units. The catalytic units do the phosphorylation, but only if the regulatory units have been knocked off by binding with cAMP.

In Aplysia sensitization, PKA phosphorylates a protein which is a K^+ channel, causing it to act more slowly. This slows re-polarization of the cell after the peak of an action potential and increases the effect of the sensory synapse. It also allows more Ca^{2+} to enter the cell, causing the release of more glutamate. (We saw in paragraph 12.3.1 how Ca^{2+} causes vesicles to release their neurotransmitter into the synapse.) The effect is sketched in part (b) of Figure 12.22. In addition, more recent research

110 I see it as the enhanced synapses' having less resistance to passage of electrochemical neuronal circuits, so that signals take the path of least resistance from one neuron to another. Physicists like minimizing paths.

111 All the discussion of Aplysia is inspired by Kandel (2006), chapter 14.

112 Bear et al., 766-67.

113 We met cAMP when we looked at how the lac operon works.

indicates the existence of a postsynaptic effect due to the installation of new glutamate receptors.[114] We will see more of this in vertebrate learning.

The Aplysia also has been the subject of the study of associative learning. In this procedure, a strong shock to the tail (the US) is associated with a gentle touch on the siphon (the CS). It is essential that the CS begin shortly before the US, which will thus come to be predicted by the CS. After repeating this association, a simple puff on the siphon brings about a much stronger response than before, more even than after sensitization. The touch, the CS, brings about an action potential in the cell and this causes release of Ca^{2+}. Since the US arrives just after the CS, the already present Ca^{2+} then causes even more cAMP to be produced in response to serotonin released by the US. More cAMP means an enhancement of the synapse which is remembered for a while after conditioning is over. So it is the CS-US coincidence which brings about the increased reaction due to synaptic strengthening in this case of associative learning. The CS causes the animal to expect the arrival of the US even when it does not.

We can note four points here:

1. This example of simple classical conditioning differs from sensitization only by the synchronization of the CS and US.
2. All three forms of short-term learning have served to increase communication between cells.
3. All three forms of learning show that already-existing synapses (due to genes and development) are modified by experience (the environment). In other words, learning depends on both genetic and environmental factors.
4. Comparison of sensitization to associative learning shows that basic forms of synaptic modification may be combined into new ones.

A similar mechanism has been found in the fruit fly, *Drosophila*, suggesting that the same process occurs across species, one more case of evolution's adopting the same solution in different species.

Since the above reactions are unconscious and weaken with time, they are examples of ***implicit***, ***short-term learning***. They should not be taken as explanations of all cases of learning, as there are other mechanisms which contribute. In other words, they may well be necessary mechanisms to learning, but not sufficient ones. Also, what we have discussed takes place at the level of axons and synapses, not at the level of cells, which remain to be explained.[115]

12.12.4. Long-term learning in invertebrates

Short-term memory is brought about by local modifications of existing synapses, when second messenger cAMP and PKA enhance glutamate release. Long-term learning, though, is a more ...well, long-term affair. This is because it requires addition of new connections which in turn need synthesis of new proteins. This requires DNA expression, which takes place only in the nucleus in the cell body and so is not due only to activity local to the synapse.

114 Bear et al., 767-68.

115 I do not understand this, but Bear et al seem to think it is an important *caveat*.

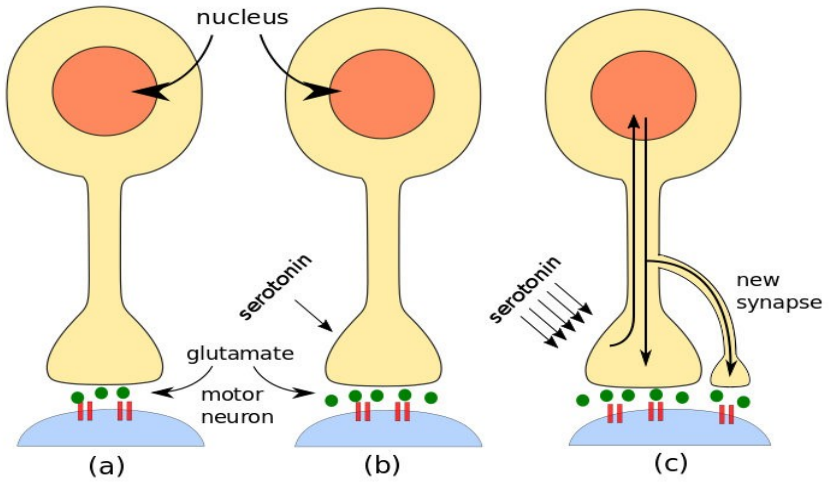


Figure 12.22: Steps in invertebrate learning: (a) simple stimulus, (b) short-term learning, (c) long-term learning. By author after Kandel.

A series of shocks to the tail of Aplysia brings about long-term learning by the additional formation of more synapses. On the molecular level, the process begins as for short-term memory. A modulating neuron releases serotonin, but more of it than in the short-term case. The serotonin from repeated shocks now activates not only PKA, but also a second kinase called ***MAP***.[116] Both PKA and MAP move to the neuron's nucleus in the cell body and influence a regulatory protein (transcription factor) called ***CREB***.[117] There are two forms of CREB:

- CREB-1 promotes gene expression and is activated by PKA;
- CREB-2 inhibits gene expression and is inactivated by MAP.

So by activation of one regulatory protein and inhibition of another, the appropriate proteins are expressed in the nucleus by processes of transcription and translation similar to those which regulate expression of the lac operon, as studied in chapter 7.[118] The proteins expressed then travel back from the nucleus to the axon where they initiate long-term synaptic facilitation through the growth of new synapses.

However, maintaining and perpetuating that growth requires proteins synthesized locally. In order to do this, inactive mRNA from the nucleus must be activated at the presynaptic axon terminal. If it left the nucleus already activated, then in a neuron which makes synaptic connections with many target neurons, the mRNA would express proteins in all the synapses. Since this facilitation must only take place on the specific axon terminal, not others, this requires yet another chemical substance to act as a switch.

A molecule called ***CPEB***[119] is found in neurons of Aplysia, Drosophila, mice and humans – and so probably every animal species. It is (or is similar to) a ***prion***, i.e., it exists in two different conformations (shapes). Serotonin causes CPEB to switch from its inactive to its active form. Since the active form is present only in the axon terminal which has been modulated by serotonin, this is what signals the proteins coming from the nucleus which axon terminals they should enhance by making new synapses. CPEB maintains local protein synthesis, in effect perpetuating the increased synaptic strength. This is selectively storing information at one synapse; it is indeed ***long-term implicit***

116 Mitogen-activated protein.

117 Creb is cyclic AMP response element-binding protein. You see why it's called CREB.

118 Obvious question: How does It know which gene to regulate?

119 CPEB is cytoplasmic polyadenylation element-binding protein.

learning (in invertebrates).[120]

It is also the only known case where the activated form of a prion serves a useful (to us) purpose. Other prions, such as those in mad-cow, or Creutzfeldt-Jakob disease, are lethal.

What we have learned about implicit learning in invertebrates: Both short- and long-term memory depend on second messenger cAMP whose synthesis is controlled by serotonin. Whereas short-term implicit learning takes place locally at synapses, long-term memory requires communication with the nucleus and expression of new proteins in order to grow more synapses and reinforce short-term changes as sketched in Figure 12.22.

12.12.5. Learning in vertebrates

A neuron will fire an action potential if its total synaptic input is above a threshold. Normally, a single input will have little or no effect, but a number of inputs can have an effect. If

1. an axon tries repeatedly to activate a cell which
2. is already strongly activated by another or other inputs at the moment when the input under question arrives,

then the synapse of the first axon with the cell is enhanced in strength. So, “neurons which fire together wire together.”

Similarly, but surprisingly, if the input arrives when the postsynaptic neuron is weakly activated, the synapse of the presynaptic neuron is diminished in strength. “Neurons that fire out of sink, lose their link.” The important thing for synaptic strengthening is the *correlation* of inputs. These two statements are a statement of what is referred to as ***Hebb's law***.[121]

We must see how such synaptic enhancement can come about and how it depends on correlation.

Studies of London taxi drivers have shown clearly that pyramidal cells in the hippocampus are the seat of spatial memory, a type of explicit memory. One way such synaptic strengthening can take place in the hippocampus is through the mechanism of ***long-term potentiation*** (***LTP***) which depends on two subtypes of glutamate receptors.

There are three subtypes of ionotropic glutamate receptors, AMPA, NMDA and kaitine, meaning that all three are activated by glutamate, but an AMPA receptor is also activated by the agonist AMPA, an NMDA receptor by NMDA and so on. Most of the fast excitatory synapses in the brain are mediated by AMPA or NMDA receptors, often coexisting at the same synapses.[122] LTP results from the synchronized firing of both.

AMPA receptors can let through Na^+ or K^+ ions, but most disallow Ca^{2+}. Under normal conditions in the brain they admit only Na^+, which is capable of quickly bringing about a strong depolarization. NMDA receptors also admit Na^+ to enter and K^+ to leave but, more importantly, they admit Ca^{2+}, one of the most important ions for cell function (for instance, in triggering presynaptic neurotransmitter release or unlocking troponin in muscles). An NMDA channel is normally blocked by a Mg^{2+} ion, which keeps the passage of Ca^{2+} minimal. Only when the Mg^{2+} is pushed out by the electromagnetic force due to depolarization of the postsynaptic membrane can Ca^{2+} enter the channel.[123] This depolarization is normally brought about by AMPA channels in the same or nearby synapses. A low-frequency action potential in the presynaptic terminal releases only moderate amounts of glutamate, so the postsynaptic AMPA receptors allow in moderate amounts of Na^+. However, a high-frequency

120 Kandel (2006), 268 ff.

121 Bear et al., 716-7.

122 Bear et al., 139, 154, 716-717.

123 Why does the electrostatic potential push out Mg2+ but allow Na+ to enter?

presynaptic action potential releases much more glutamate which in turn causes the AMPA receptors to allow in much more Na^+, depolarizing the cell. Being dependent on the depolarization is being dependent on the EM potential across the membrane, so the NMDA receptor is gated simultaneously by voltage and by glutamate. So opening of the NMDA receptor requires both pre- and postsynaptic events, making it a coincidence detector and acting like an AND gate.

Once inside the cell, Ca^{2+} acts as a second messenger and brings about a number of results. First, it causes AMPA channels already present in the interior of the cell to be inserted into the membrane of the receptor cell, thus strengthening the synapse.This is ***long-term synaptic potentiation***, usually referred to as ***LTP***, and is an example of correlated firing which strengthens synaptic coupling.

One can see how this process can lead to associations in neuronal circuits. Suppose a neuron has synapses from three inputs, say, X, Y and Z. If X fires all alone, it is incapable of depolarizing the postsynaptic cell enough for LTP to occur. The same is true for each of the other two synapses. But if both X and Y fire simultaneously, i.e., repeatedly over the same short time period, their cumulative effect may be strong enough to depolarize the cell sufficiently for LTP to take place, meaning that the X and Y synapses will be strengthened by the means we have seen. Now, if either X or Y brings an input, the postsynaptic neuron may fire, meaning that X or Y have the same result and are therefore associated. The third synapse, Z, will not have been enhanced.[124]

Another possible means of synaptic enhancement may be due to the presence on dendrites of tiny "spines", some of which have bulbous heads, which has led to their being described as shaped like mushrooms, doorknobs or even punching bags! They are thought to contribute to synaptic plasticity because they have both AMPA and NMDA receptors. They can appear and disappear, and grow and change their shape, depending on activity on both sides of the synapse. They also contain ribosomes, which are normally found near the cell body where they fabricate proteins from the recipes transcribed from DNA by mRNA. Their presence in ***dendritic spines*** is thought to be correlated with protein production which may also modulate synaptic strength. Research continues.

So LTP offers a possible beginning of an explanation of neural plasticity. Other mechanisms, such as phosphorylation of AMPA receptors, are beyond the scope of this document.[125]

A phenomenon similar to LTP, ***long-term synaptic depression***, or ***LTD***, in which AMPA receptors are removed from the synapse, explains the weakening of synapses in the case of a weakly activated synapse.

Similar mechanisms work during the modification of brain circuity during embryonic development. Cortical neurons in tissue culture spontaneously form synapses and these contain almost only NMDA receptors. Only when the synapse is strongly sollicited can depolarization occur and AMPA installation take place. So LTP can also explain the development of cortcal connectivity.

We see now that Ca^{2+} is extremely important to the organism for

- formation of bones and teeth
- neurotransmitter secretion in presynaptic cells
- muscle contraction
- neural plasticity.

Other mechanisms, such as phosphorylation of AMPA receptors, are beyond the scope of this document.

124 This excellent example is based on one given by Bear et al.

125 More in Bear et al., 772.

12.13. Overview of senses and memory

In brief, the learning process goes something like the following diagram, where we are learning what it is like to stroke a cat on our lap. The diagram shows only a schematic representation of the process, which is in reality much much more detailed.

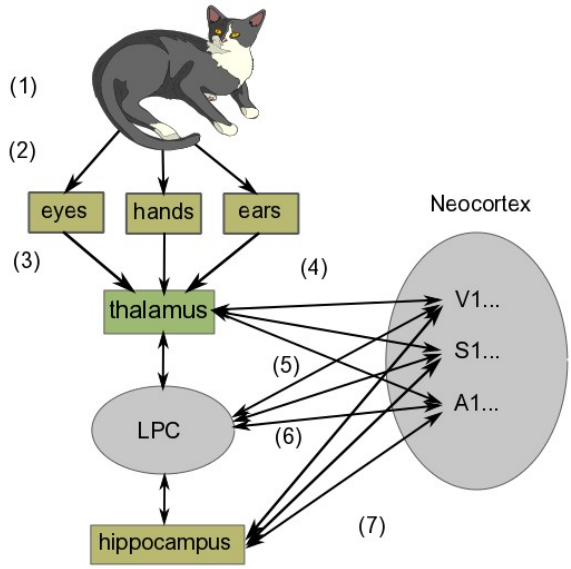


Figure 12.23: Schematic learning mechanism, by author

In order to see a greatly simplified version of what takes place in learning, we can regard it as taking place in three steps:

- Perception
    1. First, we have the cat we are looking at, listening to (if it purrs) and stroking.
    2. Light and sound waves travel to eyes and ears, somatosensory perception takes place through the fingers.
    3. Signals produced in the sense organs in the retina (seeing the cat), hands (feeling its fur) and ears (hearing it purr) are transferred to the thalamus. (If the cat had just rolled around in something smelly, which well-brought-up cats do not do, olfactory information would go directly to the olfactory cortex before being projected back to the thalamus and then relayed to the cortex for consciousness.)
    4. The thalamus routes the information to the appropriate cortex areas (Visual, Somatosensory or Auditory Areas 1 and higher) for analysis. Many scientists think that the combined activity of these areas of cortex is what constitutes the perception of the experience
- Formation of short-term memory
    5. Projections occur from the neocortex to the lateral prefrontal cortex (LPC), which creates temporary links to them. For our purposes, we may say this set of signals constitutes the image we “perceive” momentarily in our minds.
    6. The projections from the neocortex sensory areas to the LPC work in both directions. The LPC sends signals back to the cortex, bringing about activation of neurons similar

to those evoked by the original image (sight + feel + sound). But this time, rather than originating in the sense organs, the signals are coming directly from the LPC. In this way, the LPC causes the set of neuron activations (the image) to remain in the neocortex longer than it might have done otherwise. This is ***working memory***, one form of short-term memory. Most people are limited to no more than seven items at a time in working memory.[126]

- Remembering

7. The hippocampus also is connected to virtually the entire neocortex, as well as the LPC. Like the LPC, it can bring about a set of connections in the neocortex (i.e., alteration of synaptic strengths), which is at the core of thinking about the image in question. Repeated thinking like this is called ***rehearsal***. Over time (maybe several days), such rehearsal, which takes place predominantly during REM sleep[127], leads to a long-term memory of the event, again, in the same part of the sensory cortex where the original sense-data experience was stored.

12.14. Consciousness and all that

To be quite frank, it seems that not a whole lot is really known about consciousness, at least not with a significant degree of certainty. It is the subject of much conjecture by both scientists and philosophers. Some consider consciousness to be an illusion. One has suggested that consciousness may be considered as awareness expressed by language. Awareness is related to perception. Clearly, we must employ precise definitions of what all these things are.

Let's just take a quick look at what is experimentally justified for us to say about consciousness. An event of some sort out there in the environment happens and some of our senses detect it. Signals are sent over nerves to different parts pf the brain. The "different parts" is important. For vision, e.g., many different parts are involved. Then the results of the analyses of these different components are sent to the prefrontal cortex where they are somehow or other put into juxtaposition. That's all. That and only that seems to be what we can say and so that *is* being conscious of the external event. There's no image on a screen, no observer – no observing self. No self at all. It's an illusion. Whether this hypothesis is valid or not, I don't know, but it does suggest a possible understanding of what we mean when we talk about being conscious of something.

We have only briefly skimmed the surface of the subject of neuroscience. We have discussed nothing in much depth and have skipped lots of subjects, probably more than in other chapters. Among further considerations which should be taken into account are the following:

- Planning and decision making. Choice – do we have any?
- Language and speech.
- Sleep and waking.
- Emotions (and serotonin and the amygdala), on which subject whole books have been written[128].
- Repair and regeneration in the NS.

126 According to my wife, I am limited to only one – maybe two, if you include breathing.

127 Deep sleep in which dreaming is related to Rapid Eye Movement (REM).

128 Such as those of Antonio Damasio.

13. The ends – ageing and death

We have considered the end on two scales:

- Universal scale; Current theory tells us the universe will finish as particles scattered about with distances between them expanding so rapidly that any communication between them becomes impossible.
- Solar-system scale: On a firmer footing than the universal-scale theory, we know that in roughly five billion years, the sun will swell up into a red giant and engulf the earth, putting an end to whatever life may still persisted there.

On the scale of individual organisms, and in particular our favorite organism, *H. sapiens*, we know quite well that we grow old and die, but how does this come about?

Some animals, the best example being the famous Galapagos tortoises, live to be very old indeed, one having reached age 175 with only negligible senescence, probably being as healthy at 170 as at 30. Steele gives a statistical definition of ***ageing***: "… an increasing risk of death over time."[129] By this definition, Galapagos tortoises do not age for around 150 years. One can speak of their having an enhanced ***healthspan***.

It is true that we are living longer than before: Since 1840, average maximum lifespan has increased by 3 months every year.[130] This increase is presumably due to factors like better nutrition and healthcare and perhaps better protection against the challenges of nature (wild animals, natural disasters). Still, we get older and as we do, we are subjected to all sorts of diseases which people who die young do not suffer from so much.

So the question is, what causes ageing and death?

13.1. Ageing – causes and symptoms

Assuming ageing has come to be through evolution by natural selection, its many negative phenotypes occur in such a way that they do not affect reproduction but occur later in life – as is logical. Steele cites three possible mechanisms for how this occurs.

- ***Mutation accumulation***, or genetic instability: Random mutations of genes can accumulate as long as they contribute to ill health or demise only after the age of reproduction; otherwise, they would have been eliminated by natural selection. Some of these cause very serious health problems later in life.
- ***Antagonistic pleiotropy***: Evolution promotes reproduction and will trade anything in order to enhance it. ***Pleiotropy*** occurs when a single gene influences two or more different, seemingly unrelated phenotype traits. ***Antagonistic pleiotropy*** is when one trait is good and the other bad. In this case, the good one occurs early in life and benefits reproduction, so is selected (i.e., it survives), the bad one later and "benefits" sickness or death. The standard example is a gene which provides resistance to malaria but also is related to occurrence of sickle-cell anemia.
- ***Disposable soma***: ***Soma*** designates "…all the living matter of an animal or a plant except the reproductive, or germ cells."[131] The idea for ageing is that you can't have your cake and eat it too, so trade offs have to be made. Better reproduction means allocating the survival

129 Andrew Steele, Ageless: The new science of getting older without getting older.

130 Ibid, 22.

131 Encyclopaedia Britannica, "Soma", www.britannica.com/science/soma-cell. Confusingly, soma also means the bulbous part of a cell which contains the nucleus.

advantage to reproductive cells rather than soma cells, which are therefore seen as "disposable".

These three mechanisms show how ageing is not the direct result of natural selection, but rather what is left over after nature selects for other things. Natural selection is a filter, allowing those genes which contribute to reproduction to pass on to the next generation, whatever may be their effects later in life. So adverse mutations, including those resulting from antagonistic pleiotropy, may accumulate beyond reproductive age. Also, when reasonable, reproductive cells are considered more important than soma cells. By its very functioning, natural selection can not operate on phenotypes which do not affect – or occur after – reproduction. But we can.

Biogerontology is the biological study of age and its effects. The study of ageing came about with the discovery in the 1930s of ***dietary restriction*** (***DR***), which can be stated simply as, "eat less and live longer", within reasonable limits. This phenomenon has been found in numerous species, including yeast, worms, flies and other insects, mice, rats and hamsters, and dogs. DR is a good example of ***evolutionary conservation***, using and reusing the same techniques in species after species, and so must date far back in evolutionary history. The molecular machinery necessary for DR is found in every species investigated, including H. sapiens1, so it may well be universal. The important point is that it shows that ageing is not exempt from being subject to manipulation.

An example comes from the many studies of nematode worms, *C. elegans*. It has been found that two genes, age-1 and daf-2, are involved in the choice of using nutrients right away or storing them. Daf-2 is an insulin detector which, upon detecting insulin, knows that food is plentiful and signals age-1 to initiate processes of growth and reproduction – at the expense of rapid ageing. So in their normal functioning, these two genes are an aid to survival in a world where food is not always plentiful. But there is a mutated form of age-1 which changes a G nucleotide into an A, so that TGG becomes TGA and this means STOP. It's as if the age-1 was not there and this significantly increases lifespan. So what this really is, is a molecular explanation of how DR might come about.1 Thus was laboratory biogerontology born. Now it is known that there are over 1000 genes capable of increasing lifespan in various organisms.2

In order to influence the ageing process (or, rather, processes), we need to know what is going on at the molecular and cellular level during ageing. Steele suggests ten "hallmarks", of ageing. Hallmarks should have the properties that they accumulate with age and that they accelerate ageing.

1. DNA mutations and damage. These may be due to external influences like radiation or to errors in normal cell division. The most dreaded possible result of such damage is, of course, cancer.
2. Trimmed telomeres. During normal cell duplication, chromosome endings are truncated a bit. To protect against losing information, chromosomes have special endings of repeated TTAGGG patterns called ***telomeres***. After many divisions, the telomeres are shortened – ***telomere attrition*** – so much that the cell either commits apoptosis or remains ***senescent*** – not dividing any more. Short telomeres are known to be related to a number of the problems of ageing, such as diabetes, heart disease and more. Senescent stem cells in hair follicles stop making melanocytes, which means hair stops being colored and turns white.[132]
3. Protein problems. These are of three sorts.
    - Reduced autophagy. ***Autophagy*** is the cell's cleanup process, "... the natural, regulated mechanism of the cell that removes unnecessary or dysfunctional components".[133] It is the cell's house cleaning, not to be confused with apoptosis. Autophagy deficiency occurs in old age has been linked to age-related diseases. Experiments to inhibit or stop autophagy lead

132 Steele, 88.

133 Wikipedia, "Autophagy". https://en.wikipedia.org/wiki/Autophagy

to increased ageing in those favorite lab animals, worms, flies and mice. Reduced autophagy can lead to difficulty in thinking.

- ***Amyloids*** are a type of badly folded proteins. They often stick together to form plaques which inhibit normal functioning of cells and tissues. They are implicated in numerous age-related diseases, including AD (where their role is controversial), Parkinson's, other brain diseases, heart problems and diabetes.
- Protein ***adducts*** are normally formed proteins to which other molecules are bound, especially sugars (***glycation*** process) and oxygen (oxidation). Since protein function depends so much on their structure, the modified shape of adducts prevents them from working normally, leading to such problems as stiffness of eye lenses, lack of crystallin transparency (cataracts), stiffened blood vessels (leading to high blood pressure) and more.

4. ***Epigenetic alterations***, by which is meant the adjunction of molecules to the surface of DNA molecules. The commonest form is DNA methylation, which adds a methyl group (CH_3) to some location on a DNA strand, making the gene at that point unreachable for use as a protein recipe. The term also refers to the modification of how DNA is wrapped around histones, making some genes inaccessible for expression. DNA methylation is known to decrease with age, to such a degree that it can be used with great accuracy (0.96) as a "clock" to predict a person's age.[134] What is more, people whose epigenetic age is significantly greater than their calendar age tend to die young, and the reverse is true too. So ***epigenetic clocks*** are at least a measure of our health in old age, be they a cause or not.
5. ***Senescent-cell accumulation***. Most of the 40 trillion ($40x10^{12}$) or so cells in our bodies eventually wear out and stop dividing, largely because of shortened telomeres.[135] Instead of participating in continuous cell turnover via apoptosis, some resist and stick around, ***senescent*** cells. Since cancer is caused by cells multiplying excessively, senescence can be seen as an anti-cancer mechanism. On the other hand, senescent cells signal the immune system that they should be removed by secreting inflammatory molecules. This signaling is called ***SASP*** – ***senescence-associated secretory phenotype***. With age, more and more cells become senescent just at the same time – unfortunately – as the immune system weakens. The inflammatory molecules can accelerate ageing, which adds to the problem. The result is an important number of diseases associated with cellular senescence. An excess of senescent cells can occur in the brain, heart, kidneys, liver, joints, eyes (cataracts) or muscles.
6. ***Malfunctioning mitochondria***. Mitochondria are not just energy producers. They can perform fusion and fission and this may form mitochondrial networks.[136] Mitochondria produce less energy with age and, on top of that, there are fewer of them, and this is correlated with sickness and death. Mitochondria commit a kind of autophagy known as ***mitophagy*** and this also diminishes with age. So old mitochondria accumulate, just like cells or DNA, but mitochondria, of course, are inside cells. Since our brains depend on a large amount of energy produced by mitochondria, ageing can lead to lead to brain diseases like Parkinson's and AD. Some electrons may escape from the mitochondrial respiratory chain and lead to formation of highly reactive, negative ***free radicals***. It was long thought that these may accumulate and contribute to ageing, but this idea is oversimplified. It has been found that free radicals form part of the cellular communication processes, so their role is not entirely negative.
7. ***Signal failure***. The immune system's first line of defense is the inflammatory response, which

134 Steele, 96.

135 Steele, 98.

136 Wikipedia, Mitochondrial fusion. en.wikipedia.org/wiki/Mitochondrial_fusion

depends on signaling by chemokines.[137] This is one example of cell signaling and also an example of signaling which can go bad with age and lead to chronic inflammation, or ***inflammaging***. This seems to aggravate other ageing problems such as heart disease, dementia or cancer. Since such signals are transported by the blood, they can affect the whole body almost at once, leading often to simultaneous problems after a lifetime of good health. Anther signaling problem is deregulated nutrient sensing such as insulin resistance, which can leave sugar in the blood instead of storing it in liver, fat and muscle cells. Other signaling substances such as hormones vary in concentration with age and may lead to other problems.

8. ***Microbiome changes***. The ***microbiome*** is the totality of the trillions of microbes – bacteria, fungi and viruses – which inhabit our bodies especially in the gut. Among other things, they aid in digestion and fight infection, helping out the immune system. These bacteria change in concentration and in relative concentration over time and may lead to elimination problems or the already-mentioned inflammation. Like the epigenetic clock, the relative concentration of microbes in the gut can be fairly closely correlated to calendar age – accurate to several years.
9. ***Cellular exhaustion***. Especially studied are stem cells, whose activity changes with age because of several of the hallmarks already mentioned. For instance, ***hematopoietic stem cells*** (***HSCs***) in bone marrow tend to divide more often into two HSCs, rather than one HSC and one specialized cell, which increases the HSC concentration to the detriment of the normal cells they should produce, mainly red blood cells. With age ***mesenchymal stem cells*** (***MSCs***) tend to produce fat cells rather than tissue-forming cells, leading to weakening of the bones – osteoporosis and compression fractures which make us get shorter with age. Weakening stem cells are also responsible for the loss of our senses of smell and taste as we get older.
10. ***Immune system malfunction***. Once past the age of reproduction, the contribution of the immune system to keeping us alive is no longer a factor for natural selection, so old folks suffer more from infectious diseases. In this time of covid, it is unfortunate that the weakening of the immune system with age means that vaccines are not as effective, depending as they do on the manufacture of antibodies. One important factor in this decline in effectiveness is cell loss in the thymus, where T cells reach maturation. In fact, the thymus starts diminishing in size from age one! This ***thymic involution*** takes place as thymus cells turn to fat. It's disposable soma again. Hopefully, our memory immune cells, B and T, will go on defending us, but less so in the presence of new antigens. As the memory immune cells divide and redivide, they will be subject to the DNA damage already discussed and may become senescent, weakening our immune system. Interestingly, the plaques, which can block blood vessels in ***atherosclerosis*** or break up to cause ***ischemic strokes*** in the brain, are composed not simply of cholesterol goo, but of immune cells saturated with cholesterol. Macrophages may not be able to keep up with increasing amounts of cholesterol in the blood, so they gobble up more than they can really handle until they are saturated and stick together to form "foam cells", and in turn the macrophages commit apoptosis. With time, they become plaques, complex structures of different cell types surrounding a core mass of dead macrophages and cholesterol. Even mini-strokes are dangerous, as they may accumulate to reduce mental functioning, a condition know as ***vascular dementia***.

These hallmarks are not all independent. As an example, senescent cells may be due to shortened telomeres, DNA damage or cellular stress.

So ageing affects all the parts of our bodies, from DNA to proteins, from cells to tissues to organs to metabolic systems, especially the immune system.

137 See my chapter 9.7.

13.2. Experimental observations

The amazing and important thing about stem cells is that, in the words of the Nobel Prize committee, "...mature cells can be reprogrammed to become pluripotent."[138]

It was first learned from a series of experiments that placing a nucleus from a fully-differentiated somatic-cell of a tadpole into the enucleated egg cell of a tadpole led to development of a living tadpole. This shows that there is something in the egg which causes the somatic-cell DNA to essentially reboot and become ***pluripotent stem cells***, or ***PSCs***.

The mechanism behind this was discovered to be the work of four genes, transcription factors, which can convert adult somatic cells into functional ***induced pluripotent stem cells***, ***iPSCs***. The four factors are called Yamanaka factors, after the leader of the groups which isolated them. These genes allow the generation of PSCs (really iPSCs) from adult somatic cells. This is the effective inverse of stem cells' dividing to produce somatic cells, returning somatic cells to stem-cell status.

138 Wikipedia, Pluripotent stem cells, en.wikipedia.org/wiki/Induced_pluripotent_stem_cell]