Introduction to nerve cells:
Sensory receptors, synapses and spinal reflexes

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Objectives
These lectures are intended to introduce you to the electrophysiological properties of neurons in the central nervous system. After these lectures you should understand:

- The fundamental processes underlying sensory transduction and coding.
- The processes which sculpt trains of action potentials.
- The mechanisms which operate at central synapses.
- The ways in which synaptic inputs are combined to modulate spike firing.
- The principles which govern simple spinal reflexes.
- Ways in which the effectiveness of synaptic transmission can be modified.

During the remainder of the IB Physiology course you will meet many systems which embody these principles, and you should therefore make a conscious effort to relate the content of these lectures to those which follow.

Textbooks


For more depth on specific topics

TOPICS

1. The nerve cell membrane
   1.1. Introduction
   1.2. Ionic equilibria and the membrane potential
      1.2.1. The Nernst equation
      1.2.2. Distribution of Cl⁻ and Ca²⁺ ions.
      1.2.3. The Goldman equation
      1.2.4. Equivalent circuit of the nerve membrane
   1.3. The action potential
      1.3.1. Voltage-gated Na⁺ and K⁺ channels underlie the action potential
      1.3.2. The A-current spaces action potentials within a spike train
      1.3.3. Low threshold Ca²⁺ channels give rise to bursting
      1.3.4. Ca²⁺-activated K⁺ channels modulate action potential firing.

2. Sensory receptors
   2.1. Receptor current and receptor potential
   2.2. Types of sensory receptor
   2.3. Sensory coding: sensitivity, dynamic range and adaptation
   2.4. Examples of mechanoreceptors
      2.4.1. Pacinian corpuscle
      2.4.2. Muscle spindle

3. Central synapses
   3.1. Electrical versus chemical synapses
   3.2. Transmitter release
   3.3. Excitatory synapses: the EPSP
   3.4. Inhibitory synapses: the IPSP
   3.5. Interaction of EPSP and IPSP
   3.6. Presynaptic inhibition
   3.7. Neurotransmitters and neuromodulators
   3.8. Ionotropic receptors
   3.9. Metabotropic receptors
   3.10. Timescales for transmitter action

4. Neural integration
   4.1. Interaction of synaptic inputs
      4.1.1. How do synaptic inputs spread?
      4.1.2. Where is the action potential initiated?
      4.1.3. How do synaptic inputs combine?
   4.2. Spinal reflexes
   4.3. Short and long term synaptic plasticity
      4.3.1. Facilitation and depression
      4.3.2. Hippocampal Long Term Potentiation
1 THE NERVE CELL MEMBRANE

1.1 Introduction

In Part IA you learned about the basic mechanism of the action potential in axons, and the mechanism of synaptic transmission at the neuromuscular junction. In this course I will introduce you to the ways in which cells within the central nervous system interact and interconnect. One of the most dramatic features of the central nervous system is the complexity and extent of these interactions. This can be appreciated from the complicated and specialised morphologies of the dendritic arborization of cells from different locations within the central nervous system. It is within these dendritic arborizations that synaptic interactions with neighbouring neurons and incoming axons take place.

1.2 Ionic equilibria and the membrane potential

Ion concentrations and equilibrium potentials for mammalian neurons

<table>
<thead>
<tr>
<th>Ion</th>
<th>Internal concentration</th>
<th>External concentration</th>
<th>Valence ((z))</th>
<th>Equilibrium potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{Na}^+)</td>
<td>15 mM</td>
<td>150 mM</td>
<td>+1</td>
<td>+62 mV</td>
</tr>
<tr>
<td>(\text{K}^+)</td>
<td>150 mM</td>
<td>5.5 mM</td>
<td>+1</td>
<td>-89 mV</td>
</tr>
<tr>
<td>(\text{Cl}^-)</td>
<td>9 mM</td>
<td>125 mM</td>
<td>-1</td>
<td>-71 mV</td>
</tr>
<tr>
<td>(\text{Ca}^{2+})</td>
<td>(10^{-4}) mM</td>
<td>1 mM</td>
<td>+2</td>
<td>+124 mV</td>
</tr>
</tbody>
</table>

As you will remember from IA Physiology, ions are distributed asymmetrically across cell membranes. These concentration gradients are maintained in the long term by means of metabolic energy, most familiarly by the sodium pump, or sodium-potassium ATP-ase which maintains the \(\text{Na}^+\) and \(\text{K}^+\) gradients. Less familiar, perhaps, are the means by which the \(\text{Cl}^-\) and \(\text{Ca}^{2+}\) gradients are established and maintained, as detailed below.
1.2.1 The Nernst equation

If the membrane is permeable to one ion only, the potential at equilibrium can be described by the Nernst equation. As you will recall from IA, it is derived by considering the balance between electrical and chemical work as ions move down their concentration gradient. At equilibrium these two work terms are equal, so no net work is done and no net ionic flux takes place.

\[
\begin{align*}
\text{Time zero} & \quad \text{Equilibrium} \\
\text{In} & \quad \text{Out} & \quad \text{In} & \quad \text{Out} \\
K^+ & \quad \leftrightarrow & \quad K^+ & \quad \leftrightarrow & \quad K^+ \\
A^- & \quad \downarrow & \quad A^- & \quad \downarrow & \quad A^- \\
- & \quad + & \quad - & \quad +
\end{align*}
\]

\[W_c = \text{work to move 1 mole up conc. gradient} = RT \log_a \left( \frac{[K^+]_{\text{out}}}{[K^+]_{\text{in}}} \right)\]

\[W_e = \text{work to move 1 mole up elec. gradient} = zFE\]

At equilibrium \(W_c = W_e\)

\[
E = \frac{RT}{zF} \log_a \left( \frac{[K^+]_{\text{out}}}{[K^+]_{\text{in}}} \right)
\]

1.2.2 Distribution of Cl\(^-\) and Ca\(^{2+}\) ions:

To a first approximation, chloride ions are passively distributed. In other words, they distribute themselves so that their Nernst potential is approximately equal to the resting potential. Since this is close to the Nernst potential for potassium, this leads to the Donnan product rule. However, in most neurons, Cl\(^-\) is also extruded by a secondary active process coupled to the efflux of K\(^+\) ions, leading to a further lowering of Cl\(^-\) concentration. Hence \(E_{Cl}\) is normally more negative than the resting potential.

\[
E_{Cl} = \frac{RT}{2F} \log_a \left( \frac{[K^+]_{\text{out}}}{[K^+]_{\text{in}}} \right)
\]

\[
E_{Cl} = \frac{RT}{2F} \log_a \left( \frac{[Cl^-]_{\text{out}}}{[Cl^-]_{\text{in}}} \right)
\]

If chloride were passively distributed: \(E_{Cl} = E_C\)

Cancelling, taking antilogs, then cross-multiplying:

\[
\frac{[K^+]_{\text{out}}}{[K^+]_{\text{in}}} = \frac{[Cl^-]_{\text{out}}}{[Cl^-]_{\text{in}}}
\]

\[
[K^+]_{\text{out}} \cdot [Cl^-]_{\text{out}} = [K^+]_{\text{in}} \cdot [Cl^-]_{\text{in}}
\]

But in most neurons:

\[
\begin{align*}
\text{Out} & \quad \text{In} \\
\text{Na}^+ & \quad \text{ATP} & \quad \text{K}^+ & \quad \text{Cl}^- \\
\end{align*}
\]

Mechanisms for Ca\(^{2+}\) homeostasis:

\[
\begin{align*}
\text{Out} & \quad \text{In} \\
3\text{Na}^+ & \quad \text{ATP} & \quad 2\text{K}^+ & \quad 3\text{Na}^+ \\
\end{align*}
\]

Calcium ions are powerfully extruded from cells, both by an ATP-fuelled Ca\(^{2+}\) pump and by secondary active transport via a sodium-calcium exchange. These mechanisms together reduce the resting calcium concentration to below 100 nM in most cells. This enables [Ca\(^{2+}\)] to be used as an intracellular second messenger, since small Ca\(^{2+}\) fluxes will have a large influence on its concentration.
1.2.3 The Goldman equation

The Nernst equation can only be applied to the potential across a cell membrane if it is permeable to one ionic species only. However, cell membranes, even at rest, are normally permeable to more than one ion. For example, the resting membrane is predominantly permeable to K⁺ ions, so the resting potential is close to the potassium Nernst potential. However, even at rest there is a small but finite (approx 1%) permeability to Na⁺ ions, leading to a positive deviation of the resting potential from \( E_K \). This deviation can be described using the Goldman equation, which expresses the membrane potential in terms of all the ionic concentration gradients and the permeability of the membrane to each ion. It is based on the assumption that ions cross the membrane under the influence of a constant electric field.

\[
E = \frac{RT}{F} \log \left( \frac{p_K [K^+]_{in} + p_{Na} [Na^+]_{in} + p_{Cl} [Cl^-]_{in}}{p_K [K^+]_{out} + p_{Na} [Na^+]_{out} + p_{Cl} [Cl^-]_{out}} \right)
\]

1.2.4 Equivalent circuit of the nerve membrane

![Equivalent circuit diagram]

An alternative way of representing the nerve cell membrane is in terms of an equivalent circuit, containing pathways for the current carried by each of the ions present. Each such pathway contains the “Nernst battery” for that ion, and a resistor representing the conductance of the membrane to that ion. Ohm's law can be applied to each limb of the circuit to describe the total current which flows across the membrane.

Current also flows to charge the membrane capacitance whenever the voltage changes, giving rise to a capacitative displacement current.

Ohms Law: \( I = \frac{V}{R} = g \cdot V \)

Sodium: \( I_{Na} = g_{Na} (E - E_{Na}) \)

Potassium: \( I_k = g_k (E - E_k) \)

Chloride: \( I_{Cl} = g_{Cl} (E - E_{Cl}) \)

Capacitance: \( I_c = C_m \frac{dE}{dt} \)
1.3 The action potential

1.3.1 Voltage gated Na\(^+\) and K\(^+\) channels underlie the action potential

During the action potential, the permeability to Na\(^+\) ions rises explosively. Depolarization of the membrane leads to the opening of voltage-gated Na\(^+\) channels, which allow Na\(^+\) ions to enter, thus depolarizing the membrane further. This positive feedback gives rise to the all-or-none action potential, and the existence of a well-defined threshold, corresponding to the point at which inward current carried by Na\(^+\) exceeds outward current across the resting membrane.

Voltage clamp experiments in which the membrane potential is held constant reveal that the Na\(^+\) conductance activates transiently on maintained depolarization, and then inactivates. In contrast, the voltage gated “delayed rectifier” K\(^+\) conductance does not inactivate on this time-scale.

Patch clamp recording reveals the opening of the individual ionic channels which underlie these currents. The probabilistic openings of individual Na\(^+\) channels sum together to yield the macroscopic Na\(^+\) current.
Individual voltage gated channels have a characteristic structure comprising **4 subunits/repeats**, each containing **6 membrane-spanning segments**. Segment S4 acts as a **voltage sensor** controlling channel gating. The P segment between S5 and S6 is believed to form the lining of the pore.

The current-voltage relation for the Na\(^+\) conductance exhibits a region in which the channels open as a steep function of voltage, which is followed by the more gradual decline in Na\(^+\) current as the membrane potential approaches the sodium Nernst potential. At any point a line can be drawn to the sodium Nernst potential, whose slope represents the **chord conductance** for Na\(^+\).

### 1.3.2 The A-current spaces action potentials within a spike train

If an axon containing just voltage gated Na\(^+\) and K\(^+\) conductances is depolarized by injecting steady current, then the rate of firing depends extremely steeply on the magnitude of the injected current. However, if a neuron cell body is depolarized, then the rate of action potential firing is a **graded function of the injected current**. This allows a depolarizing input to a sensory receptor or a neuron to be encoded as a **train of action potentials**. To do so requires a further conductance to potassium which inactivates on maintained depolarization.
Depolarizing voltage clamp steps in the presence of a Na\textsuperscript{+} channel blocker reveal a component of K\textsuperscript{+} current which inactivates, and which can be abolished if the cell is held at a depolarized potential before the strongly depolarizing clamp step. This inactivating potassium current is known as the A-current.

Imagine a neuron which is stimulated by a steady depolarizing current. Immediately following each action potential, I\textsubscript{A} remains inactivated at first, but I\textsubscript{K} remains high for a time, holding the membrane at a negative potential. Thereafter, I\textsubscript{A} activates, preventing the injected current from raising the membrane to threshold. However, I\textsubscript{A} progressively inactivates, allowing the membrane to approach threshold and the next spike to be fired. So the A current serves to space out the action potentials in the spike train. Voltage gated K\textsuperscript{+} channels are diverse: some inactivate rapidly, others do not inactivate at all.

1.3.3 Low-threshold Ca\textsuperscript{2+} currents give rise to bursting

Low threshold Ca\textsuperscript{2+} conductance leads to bursting

Cortical pyramidal cell

Regular firing

Burst firing

Thalamic relay neuron

Burst mode

Transfer mode

-75mV

Many neurons in the CNS fire action potentials in bursts. For example, some cortical pyramidal cells demonstrate intrinsic bursting even when stimulated continuously. Bursting behaviour is generated when depolarization activates low threshold calcium channels.
Ca channels in neurons

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Name</th>
<th>Threshold</th>
<th>Inactivation</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T</strong></td>
<td>Transient</td>
<td>-65 mV</td>
<td>Moderate (20-50 ms)</td>
<td>Rhythmic burst firing</td>
</tr>
<tr>
<td><strong>L</strong></td>
<td>Long-lasting</td>
<td>-20 mV</td>
<td>Very slow (&gt;500 ms)</td>
<td>Synaptic transmission</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dendritic Ca(^{2+}) spikes</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>Neither</td>
<td>-20 mV</td>
<td>Moderate (50-80 ms)</td>
<td>Synaptic transmission</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dendritic Ca(^{2+}) spikes</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>Purkinje</td>
<td>-50 mV</td>
<td></td>
<td>Dendritic Ca(^{2+}) spikes</td>
</tr>
</tbody>
</table>

Neurons contain a number of different **voltage gated calcium channels** opened by depolarization, which normally co-exist in a single cell. **Low threshold T channels** contribute to bursting by activating as the membrane is slightly depolarized, contributing to that depolarization and encouraging spike firing, and then inactivating to terminate the burst.

### 1.3.4 Ca\(^{2+}\)-activated K\(^{+}\) channels modulate action potential firing

Ca\(^{2+}\)-activated K\(^{+}\) conductance slows spiking in a vagal motoneurone.

Action potential firing is also modulated by **Ca\(^{2+}\)-activated K\(^{+}\) channels**. These open when Ca\(^{2+}\) enters through voltage-gated Ca\(^{2+}\) channels, and contribute an outward K\(^{+}\) current which opposes the depolarization and hyperpolarizes the cell. They act to slow spike firing in response to a steady injected current, causing **spike frequency adaptation**. They also contribute to the termination of bursts of action potential firing, since each burst is accompanied by a rise in intracellular [Ca\(^{2+}\)].
2 SENSORY RECEPTORS

2.1 Receptor current and receptor potential

In a generalised sensory receptor the incident stimulus evokes a receptor current whose amplitude changes in a graded manner according to the strength of the stimulus. This receptor current results in a graded receptor potential, which depolarizes the site of impulse initiation, which is specialised to vary its rate of spike firing according to the magnitude of the depolarizing current. There are, as you will learn later in the course, exceptions to this rule, including receptors such as the rod and cone photoreceptors, which hyperpolarize on stimulation.

2.2 Types of sensory receptor

Sensory receptors can be divided into two broad categories: “long” receptors which send afferent axons to the central nervous system and which fire action potentials, and “short” receptors which do not have an axon, but which immediately transmit their signals to a second-order cell for conduction as a spike train to the CNS. “Short” receptors often generate a graded potential instead of firing spikes: there is no need to conduct the signal long distances. This leads to graded changes in transmitter release at the synapse, and (as you will learn in later lectures) a graded generator potential in the second order cell, which modulates the rate of spike firing.

In both cases the incident stimulus may be filtered by accessory structures before the sensory terminal itself is stimulated.

Some examples of “long” and “short” receptors are shown below. You will learn about their detailed properties in the courses that follow. Cutaneous mechanoreceptors are the quintessential “long” receptors, producing receptor currents in their terminals within the skin, leading to the firing of action potentials which are conducted long distances to the brain. Special senses are mostly supplied with “short” receptors. The exception is the olfactory receptor, which sends axons directly to the olfactory bulb within the brain. You will learn about cutaneous afferents in the Somatic Sensation lectures from Dr David Tolhurst, auditory and vestibular hair cells in the Hearing lectures from Dr Ian Winter, photoreceptors in my lectures on Vision, and olfactory and gustatory receptors in my lecture on Taste and Smell.
In mechanoreceptors the initial transduction process is direct, involving the opening of stretch-sensitive channels coupled to the cytoskeleton or, in the case of hearing, to more specialised structures. These allow small cations to flow into the cell, resulting in depolarization. Some other sensory receptors use a direct mechanism: most notably salt receptors in the tongue, where the stimulus is itself a permeant ion. However, most other sensory receptors use an indirect transduction mechanism, involving a second messenger cascade. You will meet detailed examples of these later in the course, most specifically in the retinal photoreceptors, and in the receptors of taste and smell. There are also, as you will soon appreciate, deep similarities with certain forms of synaptic transmission which operate via second messenger cascades.

2.3 Sensory coding: sensitivity, dynamic range and adaptation

For a brief stimulus of low amplitude, the response of a sensory receptor will normally be a faithful representation of that input. However, as the stimulus becomes stronger, the response of the receptor will begin to saturate. Thus the receptor can only operate within a relatively restricted dynamic range.

If a sensory receptor is exposed to a stimulus for an extended period then the response to this maintained stimulus normally declines: this process is known as sensory adaptation. If a small incremental stimulus is presented after adaptation to a steady stimulus, it is found that the sensitivity of the receptor is reduced. When plotted in log-linear co-ordinates, this desensitisation manifests itself for many receptors as a shifting of the response-stimulus relationship to higher stimulus strengths: curve shifting.

If you examine the ability of a human observer to detect a small increment in stimulus strength, ΔS, superimposed on a steady stimulus, S, you find that this just noticeable difference is often a constant proportion of the steady stimulus. This constant of proportionality, k, is known as the Weber fraction. For low steady stimuli, the sensitivity is limited by an internal threshold: ΔS0. The corresponding inverse variation of sensitivity (the reciprocal of the just noticeable difference) with steady stimulus strength is known as Weber's law, and is a characteristic feature of many sensory systems.
2.4 Examples of mechanoreceptors

2.4.1 Pacinian corpuscle

The pacinian corpuscle is an encapsulated nerve ending found deep within both hairy and smooth skin. It responds best to rapid changes, and especially well to vibration of a few hundred Hz. The nerve terminal itself is contained within a series of onion-skin like lamellae. The response of an intact pacinian corpuscle to a sustained stimulus consists of a transient receptor potential at the onset and cessation of stimulation, which leads to the firing of just a few action potentials. This represents an example of rapid adaptation to a sustained stimulus in this sensory receptor. However, if the lamellae are removed then the receptor potential becomes more sustained. In other words the majority of the adaptation in this mechanoreceptor results from visco-elastic relaxation of the accessory structures which form the lamellated bulb of the pacinian corpuscle. Note, however, that spike frequency accommodation of the action potential encoding region still takes place during the spike train even after removal of the lamellae.

2.4.2 Muscle spindle

The muscle spindle is a specialised mechanoreceptor in skeletal muscle. It consists of a bundle of modified intrafusal muscle fibres which are connected in parallel with the extrafusal fibres which form the muscle itself. The intrafusal fibres can be subdivided into two types: nuclear bag and nuclear chain. The muscle spindle receives both afferent and efferent innervation. The afferents can be divided into two types: the large Group IA afferents which supply the primary endings spiralling around the central part of the muscle spindle, and the Group II afferents which supply the secondary endings closer to the poles of the spindle. Each intrafusal fibre also receives motor innervation: the so-called gamma motor efferents, which can be compared to the alpha motor neurons which innervate the extrafusal muscle itself.
When the muscle spindle is stretched, deformation of the primary and secondary endings results in depolarization of their sensory terminals and the generation of a train of action potentials. However, the primary and secondary endings differ considerably in their discharge properties. The spindle secondary endings fire at a frequency which depends on their length, while the primary endings fire more rapidly while they are being stretched: in other words they respond to both length and velocity. The responses of the Group II afferents from the secondary endings are therefore said to be static, while the responses of the Group IA afferents from the spindle primary endings are said to be dynamic.

Once again, these response properties can largely be explained by the mechanical properties of the muscle spindle. The primary endings contact the dynamic nuclear bag fibres, whose nuclear region lengthens rapidly on applied stretch, but subsequently creeps back towards its original length as the viscous polar regions lengthen more slowly. In contrast, the nuclear chain fibres stretch more uniformly, giving rise to a static secondary response. Both nuclear bag and nuclear chain fibres receive gamma fusimotor innervation, which enhances the dynamic and static components of the response. You will learn more about these detailed changes in the course of lectures on the motor system.
3 CENTRAL SYNAPSES

3.1 Electrical versus chemical synapses

So how can the action potential trains conducted along a nerve axon be transmitted to another cell? One approach would be to transmit the signal electrically via a gap junction. Such gap junction channels span between the membranes of the pre-synaptic and post-synaptic cells, and allow ions and small molecules to pass freely. However, they suffer from a number of disadvantages when compared to a chemical synapse. First, they require a large presynaptic terminal in order to deliver sufficient current to depolarize the postsynaptic cell. Second, they are almost all bidirectional. Third, they do not offer the flexibility of chemical synapses, which by using different transmitter/receptor systems allow excitatory or inhibitory signals to be transmitted. Gap junctions are therefore normally used when it is necessary to synchronise the activity of large populations of cells, as in the developing embryo, or within the beating heart. The link between electrical activity and transmitter release in chemical synaptic transmission is, as you learned last year at the neuromuscular junction, the entry of Ca\(^{2+}\) ions through voltage gated Ca\(^{2+}\) channels (high threshold N and L type channels). Calcium is a good intracellular messenger for this purpose because it is normally held at a low concentration (100 nM or less) within the resting synaptic terminal. In the immediate vicinity of an open Ca\(^{2+}\) channel, a much higher Ca\(^{2+}\) concentration of 10s or even 100s of μM can be rapidly attained.

3.2 Transmitter release
Transmitter is released quantally at chemical synapses by the fusion of synaptic vesicles with the membrane of the presynaptic terminal, which is induced by the rise in intracellular \([\text{Ca}^{2+}]\). For vesicle fusion to occur, a number of events must take place. First, the synaptic vesicle must dock at the presynaptic active zone via the interaction of VAMP (or v-SNARE) with the membrane t-SNARE. Then the vesicle is primed by association with SNAP and NSF, and perhaps also the binding of synaptotagmin to the resulting fusion complex, followed by the hydrolysis of ATP. Finally, the vesicle must fuse with the plasma membrane in a \([\text{Ca}^{2+}]\)-dependent manner, releasing its contents into the synaptic cleft.

This fusion process is poorly understood at the molecular level, but appears to involve the formation of a transient fusion pore, which then breaks apart to induce membrane fusion.

Synaptic transmission can be investigated at the squid giant synapse, where postsynaptic voltage is found to be a very steep function of presynaptic depolarization. Furthermore, a graded variation of presynaptic potential and the presynaptic \([\text{Ca}^{2+}]\) current leads to a steep variation in the postsynaptic potential, reflecting the steep \([\text{Ca}^{2+}]^4\) dependence of vesicle fusion on external calcium.
3.3 Excitatory synapses: the EPSP

In IA you met the simple chemical synapse of the neuromuscular junction, which serves to relay excitation from the terminal of the motor nerve to a muscle fibre. In this case a single end plate terminal generates a sufficiently large end plate potential to reach threshold and fire an action potential in the muscle membrane. In contrast, an alpha motor neuron within the spinal cord receives thousands of synaptic terminals, for example from the spindle Group IA fibres which mediate the monosynaptic spinal stretch reflex.

Each of these afferent terminals generates only a small excitatory post-synaptic potential (EPSP) of a few hundred μV, so it is necessary to excite many afferent fibres simultaneously in order to cause the alpha motor neuron to fire. I will revisit this question in Lecture 4 when considering how synaptic potentials are combined together. For now, simply note that it illustrates a further principle of sensory and neuronal coding: the transmission of information along many parallel pathways thereby increasing the information content of the signal.

If you inject a steady current into a spinal motor neuron in order to perturb its membrane potential and then stimulate the IA afferents then you find that the EPSP changes sign at a potential of around zero mV. This implies that the excitatory post-synaptic current which gives rise to the EPSP must reverse at the same potential. This value does not correspond to the reversal potential of any single ion, implying that the glutamate-gated channel responsible for the EPSP must allow more than one ion to pass. In fact it allows both Na⁺ and K⁺ ions to flow across the membrane, giving rise to a reversal of current when the inward current carried by Na⁺ ions exactly balances the outward current carried by K⁺ ions. This is analogous to the situation which you met last year at the motor end plate, at which the acetylcholine receptor channel allowed all small cations to pass, giving rise to a reversal potential of around −10 mV. This reversal potential for the end plate current is affected by altering the external concentration of Na⁺ or K⁺, whose Nernst potentials contribute to the net current, but not the concentration of Cl⁻, which cannot pass.
3.4 Inhibitory synapses: the IPSP

Inhibition from antagonist

IPSP on stimulating 1A afferents of antagonist

Flexor

Extensor

Steady potential during current injection into motoneuron (mV)

-56

-64

-74

-82

-96

5 mV

5 mV

5 mV

5 mV

0 10 20 Time (ms)

made less negative by injecting Cl⁻ ions from the recording electrode, indicating that it is due to an elevation in Cl⁻ conductance.

So when the excitatory neurotransmitter glutamate is released from the presynaptic IA terminal, it “closes the switch” in the equivalent circuit of the postsynaptic membrane. The peak EPSP voltage will depend on the relative magnitude of the resting membrane conductance and the synaptic conductance, and the values of the two reversal potentials. The influence on the cell body will also depend on how far away along the dendritic tree the synapse is located, a topic which I will discuss in Lecture 4.

If, instead, you excite IA afferents from the antagonist muscle, then they inhibit the alpha motor neurons of the agonist, via inhibitory interneurons which release the transmitter glycine. The inhibitory post-synaptic potential reverses at −80mV, and this reversal potential is
3.5 Interaction of EPSP and IPSP

If EPSPs and IPSPs are evoked simultaneously, then the underlying synaptic conductance changes summate non-linearly. Imagine inhibitory and excitatory synapses located on the cell body. The EPSPs alone might reach threshold and fire a spike, the IPSPs alone would hyperpolarise the cell drawing it away from firing threshold. Note that in each case the synaptic conductance increase tries to draw the membrane potential towards its own reversal potential. If EPSPs and IPSPs are evoked simultaneously, then the potential is drawn to some point in between the two reversal potentials, and the resting potential of the neuron. The peak value of the net post-synaptic potential will depend on the relative magnitudes of the three conductances, and the values of the reversal potentials. The situation becomes more complicated still if the synapses are located some distance away from the cell body on the dendritic tree, as you will learn at the start of Lecture 4.

3.6 Pre-synaptic inhibition

An alternative way of generating inhibition is to form an inhibitory synapse on an excitatory synaptic terminal. This is known as **presynaptic inhibition.** The opening of channels permeable to Cl⁻ or K⁺ reduces the height of the action potential in the presynaptic terminal. The action potential height will still be decreased even if the Cl⁻ Nernst potential is slightly more positive than the resting potential, leading to a slight primary afferent depolarization, which partially inactivates Na⁺ channels.

All of these processes lead to a reduced opening of **voltage-gated Ca²⁺ channels,** and a correspondingly reduced influx of Ca²⁺. In some cases, the opening of Ca²⁺ channels can also be modulated directly by second messenger systems within the presynaptic terminal. The consequence of this reduced Ca²⁺ influx is a reduction in transmitter release: since vesicle fusion depends very steeply on Ca²⁺ concentration, a subtle change can result in a very significant decrease in transmitter release. For presynaptic inhibition to be effective, the timing of the inhibitory signal must be precise, since it must arrive at virtually the same time as the excitatory signal for inhibition to be effective. This constraint is relaxed somewhat with peptide transmitters, which have slower neuromodulatory effects than the fast excitatory and inhibitory transmitters which we have considered so far.
3.7 Neurotransmitters and neuromodulators

As was the case for sensory transduction, neurotransmitters can act either directly on **ionotropic receptors** which are themselves ionic channels, or indirectly on **metabotropic receptors** which achieve their effects via **second messenger cascades**.

A diverse range of substances act as synaptic transmitters or neuromodulators within the CNS. These can be broken down into several categories. First, there are the **amino acid transmitters**, which among their number include **glutamate**, the primary excitatory transmitter within the CNS. This class also includes **GABA** and **glycine**, the major inhibitory transmitters within the brain and spinal cord respectively. Then come the **bioactive amines**, including the **catecholamines**, **dopamine** and **serotonin**; together with **acetylcholine**, which act not only within the peripheral but also the central nervous system. Note also that **ATP** can act as a transmitter in its own right at a number of **non-adrenergic non-cholinergic** autonomous synapses, acting at **purinergic receptors**. Finally, there is an extremely diverse range of **neuropeptides**, which perform transmitter, neuromodulatory and hormonal functions, and are often **co-released** with more traditional transmitters, e.g. ACh and VIP.

For a substance to be accepted as a neurotransmitter, it must fulfil three criteria. First, it must be **present** within the presynaptic terminal, or mechanisms exist for its synthesis. Second, it must be **released** in adequate quantity on stimulation. Finally, **added transmitter** must have the same effect as stimulation.

<table>
<thead>
<tr>
<th>Transmitter</th>
<th>Symbol</th>
<th>Ionotropic</th>
<th>Metabotropic</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amino acids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glutamate</td>
<td>Glu</td>
<td>AMPA and NMDA receptors</td>
<td>mGlur₁ to mGlur₅ receptors</td>
<td>The major excitatory transmitter in the CNS.</td>
</tr>
<tr>
<td>γ-aminobutyric acid</td>
<td>GABA</td>
<td>GABA₁ receptor</td>
<td>GABA₂ receptor</td>
<td>Inhibitory transmitter; GABA₂ is CI channel.</td>
</tr>
<tr>
<td>Glycine</td>
<td>Gly</td>
<td>Glycine receptor</td>
<td></td>
<td>Spinal cord inhibitory transmitter, CT channel.</td>
</tr>
<tr>
<td><strong>Amines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>ACh</td>
<td>Nicotinic receptors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>NA</td>
<td>β₁, β₂, β₃, α receptors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td>DA</td>
<td>D₁-like and D₂-like receptors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotonin</td>
<td>5-HT</td>
<td>5-HT₂ receptor</td>
<td>5-HT₁, 5-HT₃ receptors</td>
<td>Raphe nucleus</td>
</tr>
<tr>
<td><strong>ATP</strong></td>
<td>ATP</td>
<td>P₅₃ receptor</td>
<td>P₅₄ receptor</td>
<td></td>
</tr>
<tr>
<td><strong>Neuropeptides</strong></td>
<td></td>
<td>Diverse</td>
<td></td>
<td>Opioids, pituitary peptides, secretins, insulins, tachykinins, somatostatins, gastrins.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Some families of peptide transmitters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family</strong></td>
</tr>
<tr>
<td>Opioid</td>
</tr>
<tr>
<td>Neurohypophys</td>
</tr>
<tr>
<td>Tachykinins</td>
</tr>
<tr>
<td>Secretins</td>
</tr>
<tr>
<td>Insulins</td>
</tr>
<tr>
<td>Somatostatins</td>
</tr>
<tr>
<td>Gastrins</td>
</tr>
</tbody>
</table>
3.8 Ionotropic receptors

Ionotropic receptors have a characteristic structure consisting of 5 subunits. The classic example is the nicotinic acetylcholine receptor, which is comprised of two α-subunits, each with an ACh binding site, and single β, γ and δ subunits. Each subunit consists of four membrane spanning segments, the second of which forms the lining of the channel.

The subunits of ionotropic glutamate receptors were once thought to have a very similar structure to the nicotinic ACh receptor, but it is now believed that the second transmembrane domain is actually a hairpin P segment which forms the pore lining. There are two distinct classes of ionotropic glutamate receptor: NMDA and non-NMDA (AMPA and kainate) receptors. These are named after the most potent synthetic agonists for each channel class. They differ not only in their pharmacology, but also in their ionic permeability. AMPA receptors mostly have a linear ohmic current-voltage relationship, and are mostly impermeable to divalent cations. In contrast, NMDA receptors are also permeable to Ca\(^{2+}\) ions, but at negative potentials they are blocked by extracellular Mg\(^{2+}\) ions trying to enter the channel. When the membrane is depolarized this block is relieved, so that Na\(^{+}\) and Ca\(^{2+}\) ions can pass through the channel.
3.9 Metabotropic receptors

In contrast to ionotropic receptors, which are themselves an ionic channel, metabotropic receptors are coupled to second messenger cascades by way of a G-protein. G-protein coupled receptors have a characteristic structure with 7 membrane-spanning segments, and a ligand binding site. The 3rd intracellular loop interacts with a G-protein, which binds GTP in exchange for GDP and couples to an effector enzyme. Most commonly such coupling takes place via the GTP-bound α-subunit, but an increasing number of examples have been found in which the βγ subunits act on the effector instead. Such G-protein coupled cascades can stimulate or inhibit the formation by adenylyl cyclase of cAMP, which acts via protein kinase A. You will also later on, in vision and olfaction, meet examples of sensory receptors which use cAMP or cGMP to modulate cyclic nucleotide gated channels directly. Another important second messenger is IP₃, responsible for Ca²⁺ release from intracellular stores, and via DAG the activation of protein kinase C. Finally, arachidonic acid, formed by the G-protein coupled activation of phospholipase A₂, is a candidate for a retrograde messenger to modulate transmitter release from presynaptic terminals.

The basic principle behind all of these cascades is one of amplification: one activated receptor can interact with many G-protein molecules, and one activated effector enzyme can create (or destroy) many 2nd messenger molecules.

In some cases a more direct modulation of the effector enzyme takes place. With a receptor tyrosine kinase, the receptor itself is the effector enzyme. Nitrous oxide acts directly on its effector, the soluble guanylyl cyclase. These schemes sacrifice one, or both stages of amplification for a more direct coupling between stimulus and response. They also sacrifice another key aspect of G-protein signalling: that of versatility. As you can see from the cascades above, different G-proteins can modulate a single effector enzyme in different ways.
3.10 Timescales for transmitter action

<table>
<thead>
<tr>
<th></th>
<th>1 msec</th>
<th>1 sec</th>
<th>16 min</th>
<th>10 days</th>
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</thead>
<tbody>
<tr>
<td>Fast transmission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slow transmission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facilitation/depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modulation/hormonal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trophic effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Acetylcholine (nicotinic)
Amino acids
Acetylcholine (muscarinic)
Catecholamines
Many other transmitters
Peptides and hormones
Growth factors

Different transmitters operate on very different **timescales**. The fastest are the classical amino acid and amine transmitters, acting at ionotropic receptors. Next come the classical transmitters, acting at metabotropic receptors, followed by slower neuromodulatory effects. Peptides are distinctly sluggish in comparison, while growth factors mediating neurotrophic effects are slowest of all. You will learn about some of these slower modulatory processes in lectures on neural development next term.
NEURAL INTEGRATION

Interaction of synaptic inputs

Individual neurons receive a multiplicity of synaptic inputs at different locations. For example, a cortical pyramidal cell receives synapses on the soma, on the dendritic shaft and on dendritic spines. It is possible on ultrastructural and immunohistochemical grounds to subdivide these synapses into Type I excitatory synapses, and Type II inhibitory synapses. But where should these different classes of synapses be located to have the best effect, and how do their various inputs combine to modulate action potential firing?

How do synaptic inputs spread?

\[ V = V_0 e^{-\frac{\lambda}{\tau}} \]

From Part IA, you will remember that the action potential spreads along a nerve fibre by means of local circuit currents, which raise the nerve membrane to threshold ahead of the present location of the action potential. Analysis of the cable structure of an unmyelinated nerve fibre reveals that at steady state the potential decays away exponentially with a space constant, \( \lambda \), governed by the relative magnitudes of the membrane and longitudinal resistances.

A similar analysis can be applied to the spread of synaptic current within a neuron, by splitting its dendritic tree into a number of passive cable segments into which synaptic conductances inject current when activated. Such passive cable models have achieved much in furthering our understanding of the spread of excitation and inhibition within a neuron, however recent evidence suggests that voltage-gated conductances (both to Na\(^+\) and Ca\(^{2+}\)) are present in the dendrites of many neurons, serving to boost the decaying passively conducted dendritic signal.
Where is the action potential initiated?

The action potential is initiated in a specialised region of the neuron known as the axon hillock, which has the lowest threshold for action potential firing. This can be demonstrated by recording from a single pyramidal cell in a cortical slice with two patch pipettes simultaneously (in current clamp, so that the voltage can vary freely). Irrespective of whether you stimulate through the dendritic pipette, the somatic pipette or via synapses to the apical dendrite, the action potential response is always recorded first at the soma, indicating that it is initiated there and spreads back to the dendrites. Similar conclusions were reached (in a less direct way) in the 1950s for the spinal motor neuron.

How far do synaptic inputs spread?

The extent to which a given synapse can influence the potential at the axon hillock depends on how far away from the cell body it is located along the dendritic tree. You will remember from IA that the space constant of an unmyelinated nerve varies with the square root of its diameter. This is the reason for the existence of the squid giant axon: to achieve a fast conduction velocity in an unmyelinated fibre requires an enormous diameter. In a similar way, synaptic currents will be more strongly attenuated when they flow along small diameter dendrites than when they flow along large ones.
These principles can be applied to a real neuron by considering how the potential decays from a synaptic input on the tip of one of the apical dendrites as we proceed towards the cell body. In the small dendrites there is a rapid decay in potential, but the fall becomes more gradual as we enter the larger dendrites closer to the cell body. The time to peak of the potential change also becomes slower (note log scale) as the synaptic current has to charge a progressively larger and larger fraction of the cell’s capacitance. So overall it can be seen that synaptic potentials become smaller and slower as they are conducted decrementally towards the cell body.

**How do synaptic inputs combine?**

When two excitatory synapses are activated together, their ability to stimulate the axon hillock to fire an action potential depends on how close together they are in space and time. If the **time constant** of the cell is short, then the two stimuli will need to be close together in time. If two inputs are widely separated on the dendritic tree, then the **space constant** must be long if the summed current is to reach threshold. So if two excitatory synapses are stimulated simultaneously on neighbouring dendrites, then their depolarizing currents add together. If instead an inhibitory input is activated on a neighbouring dendrite, then the currents will subtract, the inhibitory current drawing the axon hillock further from firing threshold. However, if the inhibitory synapse is located closer to the cell body on the same dendrite, then much of the excitatory current leaves before it can ever influence the cell body. Arithmetically, this is equivalent to **division**, and is often known as **shunting inhibition**. Note that hyperpolarization itself is not actually required: the important thing is that less excitatory current is available than would otherwise have been the case.

The effectiveness of shunting inhibition explains why most excitatory inputs are located further out on the dendrites, while inhibitory inputs are concentrated close to the soma. Excitatory inputs are often located on **dendritic spines**, which are believed to isolate the postsynaptic machinery both electrically and chemically from events elsewhere within the cell. The high neck resistance of many spines will, however, somewhat attenuate the excitatory current which flows into the dendrite.
Spinal reflexes

The monosynaptic spinal stretch reflex is the classic example of a reflex pathway. You have already met all of its individual components; it is now necessary to consider how they function together to perform their reflex task.
First, it is necessary to note that you are not just dealing with a single group IA muscle spindle afferent and a single α-motor neuron, but instead with a population of IA afferents and with the motor neuron pool supplying the agonist muscle. Each IA afferent will synapse with a number of motor neurons: a process known as divergence. Similarly, each motor neuron will receive synaptic inputs from a number of IA afferents: a process known as convergence. You can appreciate that convergence of excitatory input is essential for operation of the reflex, since the EPSP generated by a single IA afferent is far too small to raise the motor neuron to threshold.

All of the actions of this, and other, reflexes influencing the agonist muscle have to pass through the motor neuron pool. It is therefore known as the final common path. The finite nature of the motor neuron pool has consequences for the operation of spinal reflexes. Suppose that two strong inputs are active simultaneously, and that they stimulate overlapping populations of motor neurons. Within the overlap region there will be motor neurons which receive stimulation from both inputs, but this will result in little if any increase in firing rate: the process of occlusion. Alternatively, if two weak inputs are active simultaneously, then motor neurons in the overlapping subliminal fringe which would not be raised to threshold by either input alone may be caused to fire when both are presented simultaneously: the process of facilitation.
Inhibitory interneurons can be deployed within the spinal cord in two functionally distinct ways. In **feedforward inhibition**, the pathway to the antagonist is inhibited when the agonist pathway is stimulated. This has obvious utility in arranging for reflex inhibition of extensor muscles when flexors are reflexly stimulated. In **feedback inhibition** the excited cell contacts an inhibitory interneuron via **recurrent axon collaterals** in order to inhibit its own firing and that of its synergists. A classic example is provided by the **Renshaw cell** of the spinal cord, which serves to stabilise the level of motor neuron firing.

An example of a more complex reflex interaction is provided by the **flexor withdrawal reflex**, in which stimulation of **cutaneous nociceptors** leads to reflex extensor inhibition and flexor stimulation to withdraw the limb out of harm’s way. In conjunction, the **crossed extensor reflex** results in stimulation of the contralateral extensor and inhibition of contralateral flexor muscles in order to provide support.
Spinal reflex responses are not restricted to such “one shot” events as the tendon jerk, but also include rhythmic and co-ordinated response patterns. An example is provided by the spinal scratch reflex, in which a single stimulus results in a repetitive pattern of motor activity. One way in which such a repetitive firing pattern may be generated is by **reciprocal inhibition** between two **half-centres**, one of which excites flexor and the other of which excites extensor muscles. The reciprocal inhibitory connections ensures that only one half-centre can be active at any given time, but as its discharge accommodates over time, the other half-centre takes over. You will meet other examples of co-ordinated spinal motor responses when you learn about the control of locomotion in your lectures on the motor system.

**Short and long term synaptic plasticity**

**Facilitation and depression**

If a synapse is stimulated tetanically, transmitter release varies progressively during the stimulus train. At the frog neuromuscular junction, repeated stimulation leads to **facilitation** reflecting the progressive buildup of Ca$^{2+}$ within the terminal acting both on the vesicle release process and on release priming.

Following a period of repeated stimulation, synaptic **depression** ensues, representing both a **depletion** of the readily-releasable vesicle pool, and the action of the released transmitter on **presynaptic autoreceptors**, which act to antagonise further transmitter release. For example, in the hippocampus, GABA release is depressed by its actions at metabotropic GABAB autoreceptors, which act to hyperpolarize the presynaptic terminal.
**Hippocampal Long Term Potentiation**

At some synapses, extremely long-lasting changes in excitability can take place following stimulation. One example of such long term potentiation is provided by the synapses between the Schaffer collaterals and commissural fibres which provide spatially-segregated inputs to the pyramidal cells of area CA1 in the hippocampus. If a weak tetanic stimulus is delivered to the commissural fibres, then the EPSPs evoked by test stimuli to both pathways are unaltered. A strong stimulus to the Schaffer collaterals potentiates the EPSP in response to Schaffer, but not commissural test stimuli. However, if both are stimulated together, then both EPSPs are persistently potentiated.

Furthermore, this potentiation is not merely associative, but also obeys Hebb's law, which requires that an input is strengthened when it plays a role in firing the target cell.

The Hebbian nature of LTP at synapses in CA1 can be demonstrated by voltage-clamping the target pyramidal cell. Only when the postsynaptic cell is allowed to depolarise during presynaptic stimulation does potentiation take place. At CA1 this is believed to result from the voltage-dependent relief of Mg$^{2+}$ block at NMDA receptors opened by the released glutamate. This allows Ca$^{2+}$ to enter the cell and act on protein kinases to achieve long term changes in synaptic excitability. Thus, both transmitter and postsynaptic depolarization are required simultaneously for potentiation to take place. In addition, retrograde messengers such as NO and arachidonic acid may also act to modulate presynaptic transmitter release. At other synapses which undergo LTP, other mechanisms also operate, which may include Ca$^{2+}$ entry through some classes of AMPA receptor, and the opening of voltage-sensitive Ca$^{2+}$ channels. It is believed that LTP may underlie learning and memory: you will learn more about this role in courses later in the year.