Electrical Communication of Cells
Nerve Conduction 1 and 2
Lecture notes

Neurons and Action Potentials

The neuron is the basic functional unit of the nervous system (Fig. 1). It relays information from one part of the animal to another. A typical neuron may have between 10^3 and 10^5 synapses and may receive information from up to 10^3 other neurons.

There are three basic kinds of neurons:

1. **Afferent or sensory neurons** have sensory receptors at their peripheral ends and transmit information from physical and chemical stimuli to the central nervous system (CNS).
2. **Efferent or motor neurons** transmit signals from the CNS to muscle and gland cells.
3. **Interneurons** relay signals between neurons and comprise approximately 99% of all neurons.

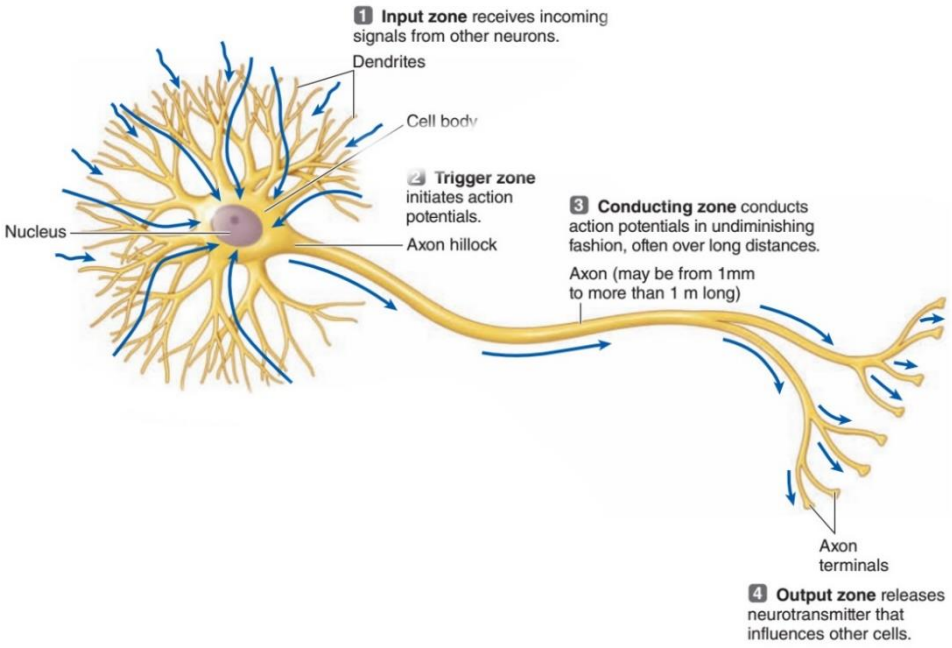

Figure 1: The structure of a neuron. (Reference: Sherwood p95)

Resting membrane potential

Membrane potential is a measure of the electrical charge across the plasma membrane of a cell. It is a feature of all cells that is determined by the differences in ion concentrations between the extracellular fluid (ECF) and the intracellular fluid (ICF), on each side of the plasma membrane, and by the relative permeability of the cell membrane to different ion species especially sodium (Na^+) and potassium (K^+) (Fig. 2). The ICF has a higher concentration of K^+ and a lower concentration of Na^+ compared to the ECF. The permeability of K^+ through the plasma membrane is also about 25-30 times higher than Na^+. Due to higher amount of large negatively charged molecules inside the cell relative to the ECF, the electrical charge inside the cell is negative.

(a)

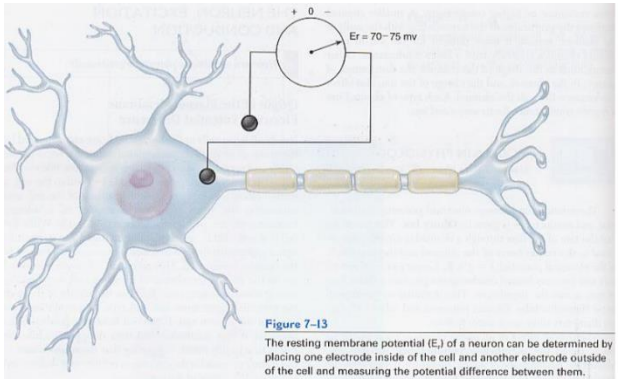

Figure 7–13
The resting membrane potential (E_r) of a neuron can be determined by placing one electrode inside of the cell and another electrode outside of the cell and measuring the potential difference between them.

(b)

Ion	Extracellular Concentration*	Intracellular Concentration*	Relative Permeability
Na^+	150	15	1
K^+	5	150	25–30
A^-	0	65	0

*Concentration expressed in millimoles per liter, mM

Figure 2: (a) Resting membrane potential. Reference: Rhoades and Planzer p222; (b) Concentration and permeability of ions responsible for membrane potential in a resting nerve cell. Reference: Sherwood p80.

The membrane potential at which the electric force is equal in magnitude but opposite in direction to the concentration force for a particular ion is called the **equilibrium potential**. In neurons, the equilibrium potential for potassium is -90 mV (inside the cell being negative) and the equilibrium potential for sodium is +60 mV (inside the cell being positive).

The **resting membrane potential** (RMP) is achieved when there is a balance in the electrical force and the concentration force for both K^+ and Na^+. The RMP of neurons is about -70mV. In the resting state, the plasma membrane is much more permeable to K^+ than Na^+ therefore, the RMP is largely determined by the ratio of the concentration of K^+ on each side of the cell membrane and is close to the equilibrium potential for K^+. The RMP does not reach the equilibrium potential for K^+ because a small amount of Na^+ moves into the cell down its concentration gradient. For a given concentration gradient, the greater the permeability to an ion species, the greater the contribution that ion species will make to the membrane potential.

Three membrane proteins play central roles in the maintenance of the RMP and in the generation and propagation of action potential. **Voltage gated ion (sodium or potassium) channels and the sodium-potassium ATPase pump (Na^+- K^+ pump).** *A detailed consideration of these three proteins is given in another lectures (Movement of molecules across cell membranes) and should now be thoroughly revised.* When neuron is at rest, the voltage gated ion channels remain closed. Because there is net movement of Na^+ into the cell and K^+ out of the cell, the concentration gradients across the nerve cell membrane would run down if it were not for the Na^+ - K^+ pump which pumps three Na^+ out for every two K^+ ions it pumps into the cell. In this way, the Na^+ - K^+ pump, by maintaining the concentration gradients across the nerve cell membrane, makes an essential indirect contribution to maintaining the RMP. In other words, as long as the concentration gradients remain fixed, and the ion permeabilities of the plasma membrane do not change, the RMP will remain constant. Most neurons have 100-200 sodium-potassium pumps per μm^2 area of membrane surface, but in some specific areas their density can up to 10 times higher.

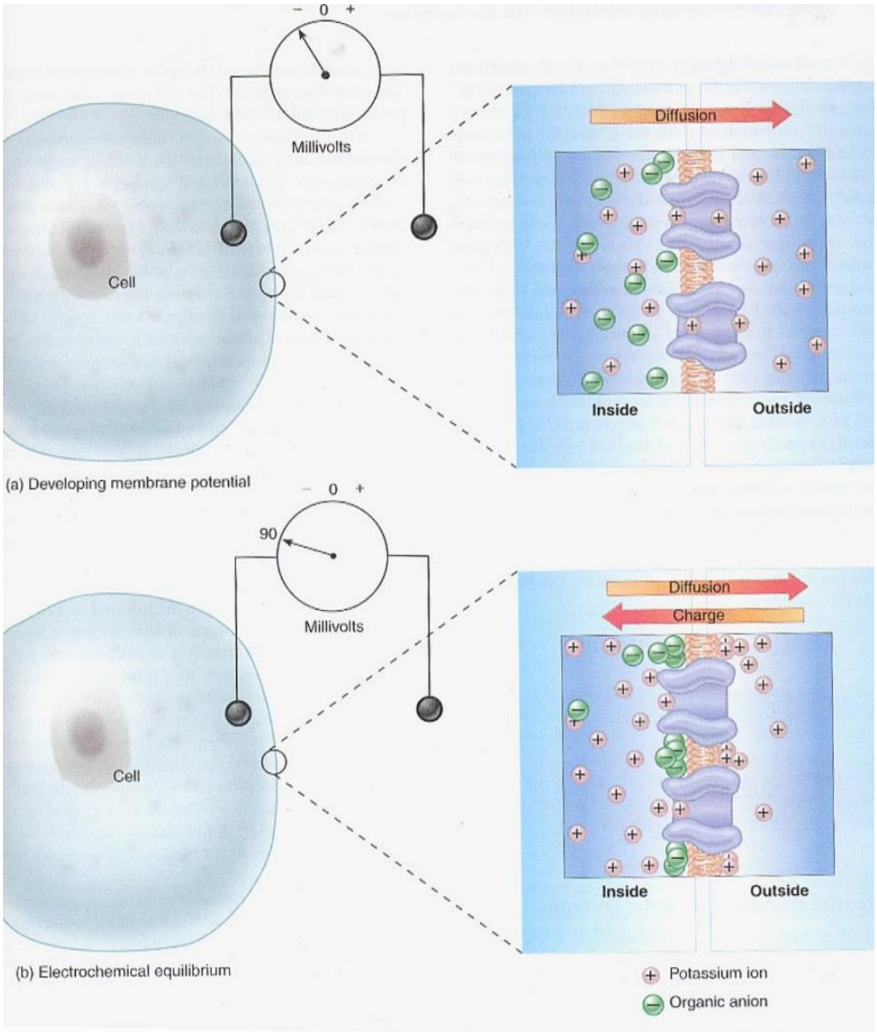

Figure 3: Ionic basis for membrane potential. Reference: Rhoades and Planzer p223.

Action Potential

For signals to be transmitted, a self-propagating change in RMP must occur across the axon membrane. An action potential is a sudden rapid change in the membrane potential which progresses along the cell membrane of the neuron. Action potential is a feature of excitable cells such as neurons and muscle cells. Action potential is an ALL OR NOTHING EVENT. Thus, once the membrane is depolarized to threshold, the rapid change in membrane potential will occur at an equal amplitude along the axon. During action potential, the membrane potential changes from -70mV to +30 mV and then repolarizes to its original value, completed in one millisecond (Fig. 4).

Ionic basis of the action potential

1. **Resting state:** K^+ channels in the membrane are open but almost all Na^+ channels are closed so that the RMP is maintained at about -70mV.
2. **Slow depolarisation:** In response to a triggering event, some Na^+ channels open allowing Na^+ to enter the cell. The membrane potential becomes more positive and approaches the threshold potential.

3. **Rapid depolarization:** As membrane potential reaches the threshold level, the voltage gated Na_+ channels open in large numbers and there is massive influx of Na^+ into the cell. The inside of the cell become even more positive, approaching but does not quite equal to the equilibrium potential for Na^+.
4. **Repolarisation:** Voltage gated Na^+ channels spontaneously close and voltage gated K^+ channels open allowing K^+ to flow out of the cell. Only a tiny portion of the Na^+ and K^+ ions in a nerve cell (~ one in 10^6) flows across the axon membrane during the action potential. Thus only a tiny fraction of the Na^+ - K^+ gradient is dissipated so the action potential is a very efficient means of signalling over large distances.
5. **After hyperpolarisation:** The voltage gated K^+ ion closes slowly allowing the flow of K^+ into the ECF causing the membrane potential to become more negative than the RMP. Na^+ - K^+ ATPase pump will then pump Na^+ out of the cell in exchange for K^+ into the cell to restore the RMP.

Conformational changes in channel proteins form the basis for gating as they serve to open and close the channels by slight movements of critically placed portions of the molecule that unblock and block the pore. In the case of Na^+ channels, the open state, which lasts about one millisecond, converts into an inactive closed state, which reverts on repolarization to a closed but activatable state.

Threshold

Action potentials can only occur when the membrane is sufficiently depolarized i.e. there is a net movement of positive ions inward. The membrane potential at which this occurs is called the threshold potential (Fig. 4).

Refractory period

After an action potential the axon membrane is unresponsive for a short period and is said to be refractory to a second stimulus. There is an absolute refractory period (during the time of Na^+ permeability changes) and a relative refractory period (during the time of K^+ permeability changes).

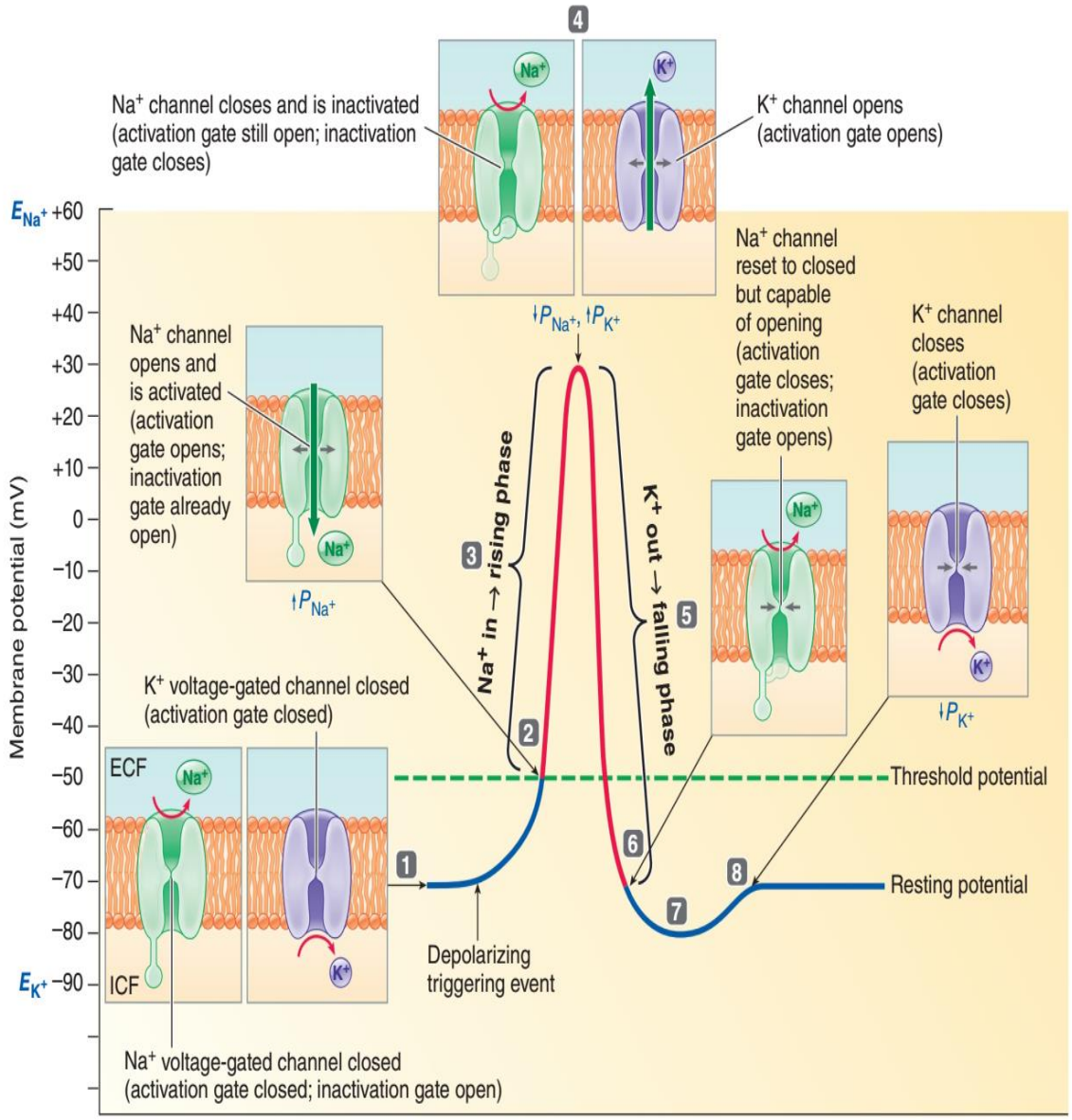

Figure 4: Ionic fluxes and changes in membrane permeability to Na+ and K+ ions during an action

Propagation of Action Potentials and graded Potentials

Each action potential triggers a new action potential at an adjacent area of membrane by local current flow. The new action potential is identical to the previous one so that no distortion of the signal occurs as successive action potentials spread along the axon membrane. Current will also flow towards the original site of stimulation from adjacent sites, however the membrane sites that have just undergone an action potential are refractory and cannot undergo another so that the only direction of action potential propagation is away from the stimulation site. Note that action potentials in skeletal muscle cells are initiated near the middle of the cell and spread to both ends whereas in most nerve cells (efferent neurons and interneurons), action potentials are initiated in the axon hillock, close to the cell body, and are propagated towards the terminal end of the neuron.

Velocity of propagation of action potentials

The velocity of propagation of action potentials is determined by the diameter of the axon and whether or not the neuron is myelinated. The larger the diameter the faster the velocity, and myelinated neurons by insulating the neuron and reducing current leak, conduct nerve impulses at a much faster rate than non-myelinated neurons. In myelinated neurons the action potentials "jump" from one node of Ranvier to the next, the process being called **saltatory conduction**. In large myelinated neurons like the motor neurons which supply skeletal muscle the velocity of propagation of action potentials is around 120 m/s.

Graded potentials

Graded potentials are local changes in RMP which occur over short distances. Their amplitude is variable and is related to the magnitude of the stimulus which produces the change in RMP, and they can be either depolarizing or hyperpolarizing. They are called graded potentials because their amplitude is directly related to the intensity of the stimulus which produces them. Because the axon membrane is so leaky when conducting current, the amplitude of graded potentials decreases rapidly with increasing distance as they fade out.

Synapses

Neurons share the biochemical machinery of all other living cells and apart from their specialized ability to transmit action potentials they also have the ability to synthesize and release a specialized array of chemical messengers known as neurotransmitters. Synapses are the microscopic regions of close proximity between the terminal end of one neuron (presynaptic neuron) and the receiving surface of another neuron (post-synaptic neuron) (Fig. 5). The arrival of an impulse causes a sudden release of molecules (neurotransmitter) from the terminal. The neurotransmitter then diffuses across the fluid filled gap between the two cells and act on specific receptor sites in the postsynaptic membrane, thereby altering the electrical activity of the receiving neuron. A postsynaptic neuron may have thousands of synaptic junctions on the surface of its dendrites or cell body e.g. a single motor neuron in the spinal cord probably receives around 15,000 synaptic endings and some neurons in the brain may receive more than 100,000 synapses. Their output will reflect the sum of all the excitatory and inhibitory synaptic inputs that they receive.

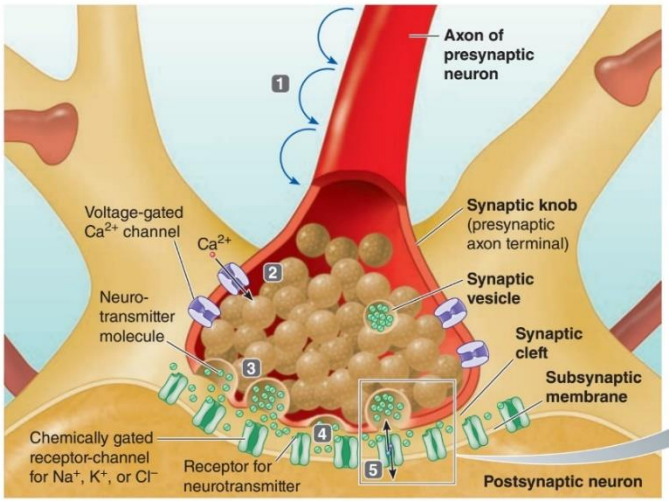

Figure 5: The structure of a synapse. Reference: Sherwood p105.

Excitatory and inhibitory synapses

Two kinds of synapses, excitatory or inhibitory, occur depending on the effect that neurotransmitter-receptor binding has on the postsynaptic membrane (Fig. 6). When it increases the permeability to Na^+ so that Na^+ flows down its concentration and electrical gradient, there is a net movement of positive ions into the postsynaptic cell bringing its membrane potential closer to threshold. This small depolarization is called an excitatory postsynaptic potential (EPSP). An inhibitory postsynaptic potential or IPSP lessens the likelihood that a postsynaptic cell will generate an action potential because the neurotransmitter-receptor binding increases thepermeability of the postsynaptic membrane to K^+ or Cl^+, but not to Na^+, so that the membrane potential moves closer to the K^+ equilibrium potential (the postsynaptic membrane is hyperpolarized) and further away from threshold.

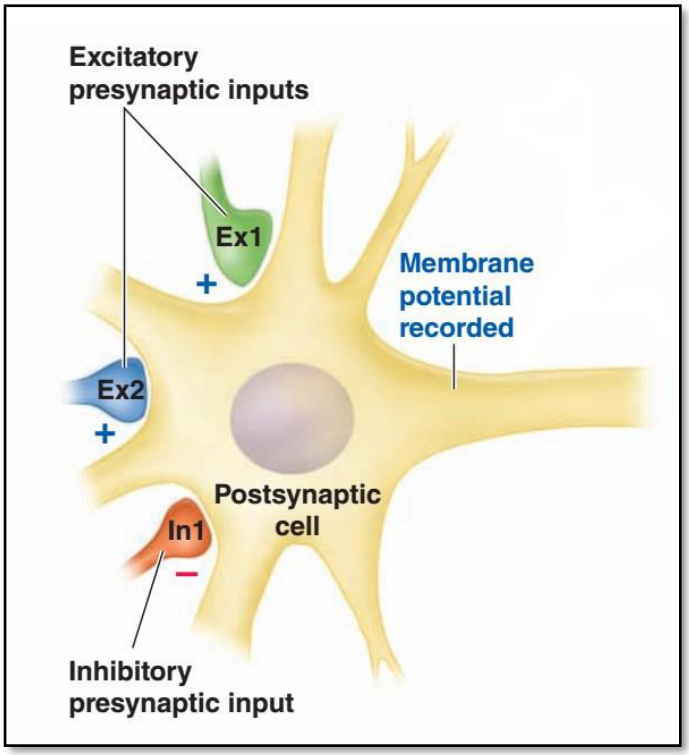

Figure 6: Presynaptic inputs Reference Sherwood p109.

Postsynaptic integration

Integration is possible because one EPSP of about 0.5 mV is not, by itself, sufficient to bring the RMP to threshold. The combined effect of a large number of temporally and or spatially summated EPSPs, balanced by similar events with respect to IPSPs (which may even cancel out the EPSPs) will determine the final outcome on the postsynaptic neuron (Fig. 7). Furthermore, the postsynaptic cell body frequently has a RMP closer to threshold in the region of the initial segment so that the location of the synapse is also important in determining the outcome. The function of inhibitory neural networks is to act as brakes on the entire nervous system, preventing a runaway spree of neural firing, and also to “fine tune” the specific responsiveness of the excitatory networks that convey and interpret information about the external world.

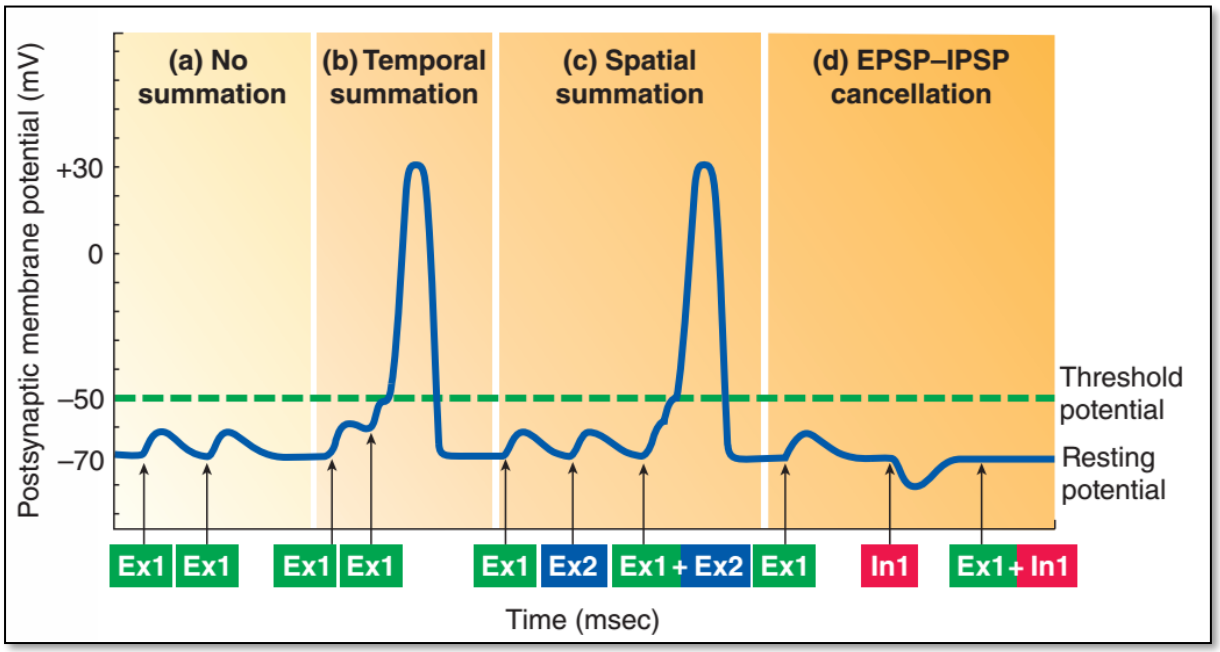

Figure 7: Post synaptic potentials. Reference: Sherwood P109.

Synaptic effectiveness

Synaptic effectiveness is influenced by any event which alters the amount of neurotransmitter released in response to an action potential in the presynaptic neuron. The more neurotransmitter released, the greater the amplitude of the EPSP or IPSP and thus the greater the number of action potentials produced in the postsynaptic neuron. Some factors which can affect the amount of neurotransmitter released include the amount of residual Ca^{++} within an axon terminal after a burst of action potentials, and presynaptic synapses from other neurons can influence the amount of Ca^{++} in the axon terminal by an effect on Ca^{++} channels in the axon terminal membrane.

Axonal transport systems

The synthesis of many enzymes and other complex molecules by the neuron can only occur in the cell body so that there is a constant movement of proteins and other components from the cell body down the entire length of the axon. The axoplasm is, in fact, an artery for a busy molecular traffic moving in both directions between the cell body of the neuron and its axon terminals. A slow-transport system moves material away from the cell body at about 1 mm/day and a fast-transport system moves material in both directions at about 10-20 cm/day. Transport systems are believed to involve the large number of fibrous proteins which are present in the axon.

Neurotransmitters

There are three criteria which a substance must meet in order to qualify as a neurotransmitter. (1) Microinjection of the proposed transmitter into the synaptic cleft must elicit the same response as stimulation of the presynaptic nerve. (2) Presynaptic nerve terminals must be rich in the proposed transmitter e.g. isolation of synaptic vesicles containing the putative neurotransmitter. (3) The presynaptic nerve must release the postulated transmitter at the right time, and in sufficient amount, to act on the postsynaptic nerve. Substances which meet these requirements include acetylcholine, the catecholamines (adrenaline, noradrenaline and dopamine), gamma-aminobutyric acid (GABA) and the amino acid glycine.

Acetylcholine is the neurotransmitter at the neuromuscular junction in skeletal muscle and at parasympathetic junctions, while noradrenaline is the neurotransmitter at sympathetic junctions on smooth muscle cells. GABA and glycine inhibit the generation of action potentials in the CNS by opening chloride channels. Additional likely neurotransmitters are the monoamines serotonin and histamine, the amino acids glutamate and aspartate, and peptides such as encephalins, and endorphins.

Acetylcholine is synthesized near the presynaptic end of axons by the transfer of an acetyl group from acetyl CoA to choline in a reaction catalysed by *choline acetyltransferase*. Some acetylcholine is taken up by synaptic vesicles and some remains in the cytoplasm. Acetylcholine is released from the presynaptic membrane quantally (in packets of 10^4 molecules). Miniature end plate potentials of 0.5 mV are continuously occurring at the motor endplate due to the random release of one vesicle containing 10^4 molecules. A full action potential is produced at the motor endplate when up to three hundred vesicles of acetylcholine are released in less than one msec. Release of acetylcholine is produced by voltage-gated Ca^{++} channels opening and allowing Ca^{++} from the ECF to flow into the presynaptic terminal resulting in the fusion of vesicles with the presynaptic membrane and the extrusion of acetylcholine by exocytosis.

The interaction of acetylcholine with specific receptors on the postsynaptic membrane changes the ion permeabilities of the membrane. The conductance of both Na^+ and K^+ increases markedly within 0.1 msec and there is a large inward current of Na^+ and a smaller outward current of K^+ producing an action potential. This change in ion permeability is mediated by the nicotinic acetylcholine receptor (hereafter referred to as the acetylcholine receptor) and although almost equally permeable to Na^+ and K^+ it allows a much greater influx of Na^+ because the electrochemical gradient for Na^+ is much steeper.

The acetylcholine receptor channel contains two non-interacting binding sites for acetylcholine and the channel can only open if both binding sites are occupied. After a short period of activity, the liganded receptor becomes inactive just as the Na^+ channel becomes inactive after it is opened by depolarization. Rapid turn off being a characteristic of nearly all signal transduction systems. This desensitization is reversible. Acetylcholinesterase hydrolyses the acetylcholine to acetate and choline and lowers its concentration. Thus the channel is designed to open and then automatically shut after a pulse of acetylcholine. The acetylcholine receptor channel is formed by five homologous transmembrane subunits and the binding of acetylcholine to its two alpha subunits opens the cation conducting pore.

References

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2. Sherwood, Human Physiology, From cells to Systems, Ninth Edition, Chapter 4

3. Stryer, L. Biochemistry. Chapter 37, pp 949-957. Chapter 39, pp 1011-1027.

4. Stephens, C.F. The Neuron. Scientific American 241: 48-59.