NEURONS, ACTION POTENTIALS, AND SYNAPSES

Simo S. Oja and Pirjo Saransaari
University of Tampere Medical School, Finland, and Tampere University Hospital, Finland

Keywords: neurones, glial cells, membrane potentials, ion pumps, information transfer, synaptic function

Contents

Summary

The different cell types in the nervous system are briefly introduced. The basis of membrane potentials is dealt with together with the genesis of action potentials. The general properties of the junctions of nerve cells—synapses—are described as well. Furthermore, the two main classes of synaptic receptors—ionotropic and metabotropic—are overviewed, with a brief description of their functional principles.

1. Introduction

1.1. Nerve Cells

There are two principal classes of cells in the nervous system: nerve cells (neurons) and glial cells. The number of neurons in the human brain has been estimated to be of the order of 10^{11}, however, glial cells far outnumber neurons by 10- to 50-fold. Neurons are in contact with other neurons by means of synapses. A typical neuron possesses 1000–2000 synapses, and a similar number of synapses originating from other neurons is attached to its plasma membrane, though these numbers vary tremendously from neuron to neuron. A typical neuron possesses morphologically distinct parts: the cell body (soma), axon (neurite), and dendrites and synaptic terminals (nerve endings) (see Figure 1). All these regions have roles in information transfer (i.e., generation of action potentials and communication of these signals from cell to cell). The cell body is the principal metabolic center that, together with the cytoplasmic endoplasmic reticulum,

produces proteins needed in the signal handling. Furthermore, it gives rise to the axon, a long tubular appendage, and the arbor of dendrites. The initial segment of an axon, the axon hillock, is the site for triggering action potentials that spread over the whole neuronal plasma membrane and propagate to the nerve endings. A great number of axons are wrapped in a myelin sheath, a protein–lipid complex made up of many layers of the membrane of Schwann cells or oligodendrocytes. This myelin sheath envelops the axon except at the nodes of Ranvier. The end region of the axon is also unmyelinated.

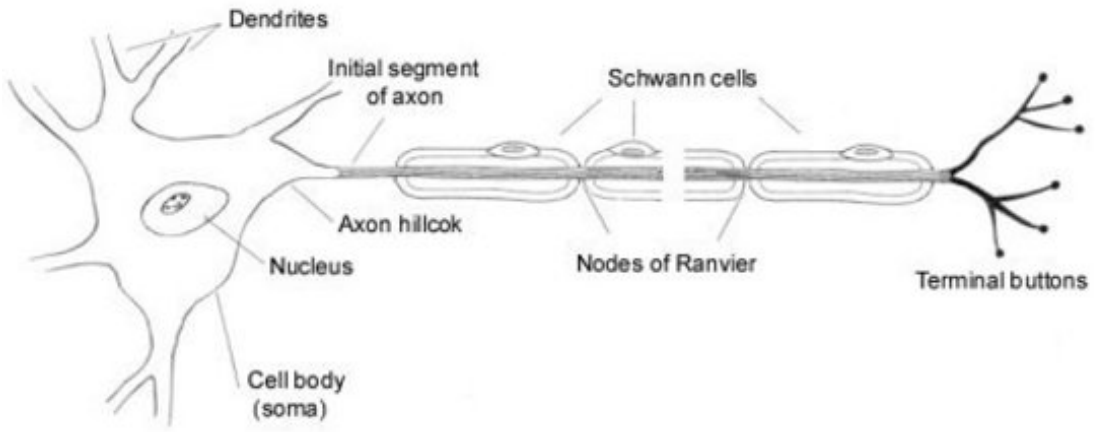

Figure 1. A typical peripheral neuron with Schwann cells wrapping its axon with the myelin sheath
Note: The myelin sheath is discontinuous at regular intervals (nodes of Ranvier).

1.2. Glial Cells

Glial cells are classified into microglia and macroglia. Microglia are phagocytes activated by infections and injury. Three types of macroglial cells abound in the vertebrate nervous system. The star-like astrocytes are the most numerous. Two subtypes of astrocytes are present. Fibrous astrocytes are found primarily in the white matter. Their name arises from the content of many intermediate filaments. Protoplasmic astrocytes, abounding in the gray matter, have granular cytoplasma. Oligodendrocytes and Schwann cells are both small in size and have scant processes. Oligodendrocytes are predominant in the central nervous system and Schwann cells in the peripheral nerves. Although not directly participating in impulse transmission, the glial cells are thought to have other important roles:

Astrocytes participate in the maintenance of ionic homeostasis and re-uptake of neurotransmitters. At least in this manner they also participate in the processes of information transfer, though probably not being involved in electrical signaling.

- Oligodendrocytes and Schwann cells produce myelin that electrically insulates axons.
- Microglial cells are involved in the defense responses to noxious factors.
- Astrocytes aid in forming the blood–brain barrier, so regulating the passage of substances from blood to brain.

- During brain development glial cells guide the migration of neurons into their final destinations.
- Glial cells also form a supporting network for neurons, a function considered to be their only role in the past.

2. Resting Membrane Potential

The uneven distribution of electrically charged particles with limited permeabilities is the basis for generation of potential differences across the cell plasma membranes (see *Ionic Channels of the Excitable Membrane*). Neurons employ this general propensity of all cells for their specific actions in information transfer. There obtains about a –65 mV potential in a typical resting neuron (i.e., the inside of the cell is negatively charged in comparison with the outside). The phospholipid bilayer in the plasma membrane is selectively permeable to Na^+, K^+, $Cl^–$, and Ca^{2+}, and practically impermeable to predominantly negatively charged proteins of large molecular size. The concentration of Na^+ is large outside the cell, whereas K^+ and Ca^{2+} are enriched inside. Two ionic pumps are particularly important for the functions of nerve cells: the Na^+–K^+ pump and the Ca^{2+} pump. Both are able to transport ions against their concentration gradients by means of chemical energy derived from the breakdown of adenosine triphosphate (ATP). The ion channels in plasma membranes are selectively leaky for the above ions. Gradually they would allow an equilibration of the ionic gradients without the continuous functioning of these ion pumps, which in this manner maintain the membrane potential and nerve cell functions.

One can calculate the equilibrium potential for each ion by knowing its charge and concentration ratio across the plasma membrane from the classical Nernst equation familiar from physical chemistry:

$$E_{ion} = 2.303\ (RT/zF)\ \log [ion]_o/[ion]_i \qquad (1)$$

in which E_{ion} is the ionic equilibrium potential, R the gas constant, T the absolute temperature, z the electrical charge of the ion, F the Faraday constant and $[ion]_o$ and $[ion]_i$ the ion concentrations outside and inside the cell, respectively. However, in this equation there is no term of the ion permeability. Moreover, the calculated equilibrium potentials for different ions are not identical and the actual membrane potentials registered from cells are a sum function of the equilibrium potentials of different ionic species. These matters are taken into consideration in the Goldman equation:

$$E_m = 61.54\ \log \{(P_K[K^+]_o + P_{Na}[Na^+]_o)/(P_K[K^+]_i + P_{Na}[Na^+]_i)\} \qquad (2)$$

in which E_m is the membrane potential of the cell, P_K and P_{Na} are the membrane permeabilities of K^+ and Na^+, respectively, and the other terms are the intracellular and extracellular concentrations of K^+ and Na^+ as in the above Nernst equation. In this Goldman equation the minor contributions of $Cl^–$ and Ca^{2+} are overlooked.

In resting neurons, the permeability of K^+ exceeds that of Na^+. Consequently, the membrane potential of a neuron is near to the equilibrium potential of K^+. Since the concentration of K^+ inside the cell greatly exceeds the extracellular concentration, the

inside of a cell is negative in comparison to the outside. On activation, the permeability of the plasma membrane to Na^+ abruptly increases several 100-fold. The membrane potential tends to approach the equilibrium potential of Na^+. Since the extracellular concentration of Na^+ is far greater than the intracellular concentration, the equilibrium potential of Na^+ is about +60 mV in a typical neuron, estimated by means of the Nernst equation for Na^+. The membrane potential of a neuron is reversed and also shortly becomes positive. It is said that there obtains an overshoot during the peak action potential. This abrupt increase in Na^+ permeability originates from the functional properties of voltage-dependent Na^+ channels in plasma membranes. These channels exhibit a characterized pattern of behavior:

- they are very fast to open,
- they stay open for about only 1 ms and close again, and
- they do not open again before the membrane potential is restored to a negative value.

These properties determine the behavior of a neuron. When the membrane potential is lowered to a certain level—the excitation threshold—the Na^+ channels are suddenly opened and the action potential ensues. The neuron is depolarized.

3. Action Potential

The action potentials obey the "all or none" law—once a stimulus is strong enough to exceed the threshold of excitation a fully fledged action potential ensues. If the stimulus is subthreshold in magnitude, it results only in a local lowering of the membrane potential, which does not propagate along the neuronal plasma membrane. An action potential is self-propagating in nature. It electrotonically depolarizes the membrane regions in front of it, spreading circularly in all directions from the site of its origin and also traversing the axon in both up and down directions. While the conduction of impulses occurs in unmyelinated nerve cells in this manner, the mode of impulse propagation in myelinated neurons is saltatory in nature. Depolarization in them jumps from one Ranvier node to the next. In this manner the velocity of conduction is greatly increased in thick axons, but not in tiny axons. These latter axons are, therefore, mostly unmyelinated. In general, in both myelinated and unmyelinated axons the conduction velocity is greater if the axon is thicker. In a living animal, nerve impulses pass in one direction only along the axons: from receptors or synaptic junctions to the synaptic terminals of the axon. Such a type of conduction is called orthodromic. An axon is able to conduct action potentials also in the opposite direction. This type of conduction is antidromic. Chemical synapses transmit impulses in only one direction, and. therefore antidromic depolarization waves wane when they meet the first synaptic site.

The increase in Na^+ permeability rapidly declines after the initiation of an action potential and the permeability of K^+ also temporarily increases after a small delay (Figure 2). At the end of an action potential the permeability for K^+ soon becomes even greater than in the resting cell, being the reason for a small but prolonged after-hyperpolarization. During the abrupt increase in Na^+ permeability, a neuron does not respond to new activation. This period is designed as an absolute refractory period. It limits the firing rate of a neuron to about 1000 Hz. In addition, it is difficult to initiate

another action potential in a neuron for several milliseconds after the absolute refractory period. This relative refractory period coincides with the negative after-potential owing to the temporarily increased K^+ permeability. During action potential neurons lose some K^+ and gain Na^+, but only prolonged trains of depolarizations result in measurable changes in the ionic concentrations. The capacity of the Na^+–K^+ pump in plasma membranes is normally able to compensate for the leakage through ion channels. The function of the Na^+–K^+ pump is electrogenic in nature, since for three Na^+ extruded from the cell two K^+ are taken up. The coupling ratio of the pump is thus 3:2 and three positive charges move out the cell for the two moving in. An increase diminishes and a decrease in extracellular Ca^{2+} increases neuronal excitability. The reason for this is the availability of Ca^{2+} for the processes associated with the synaptic events.

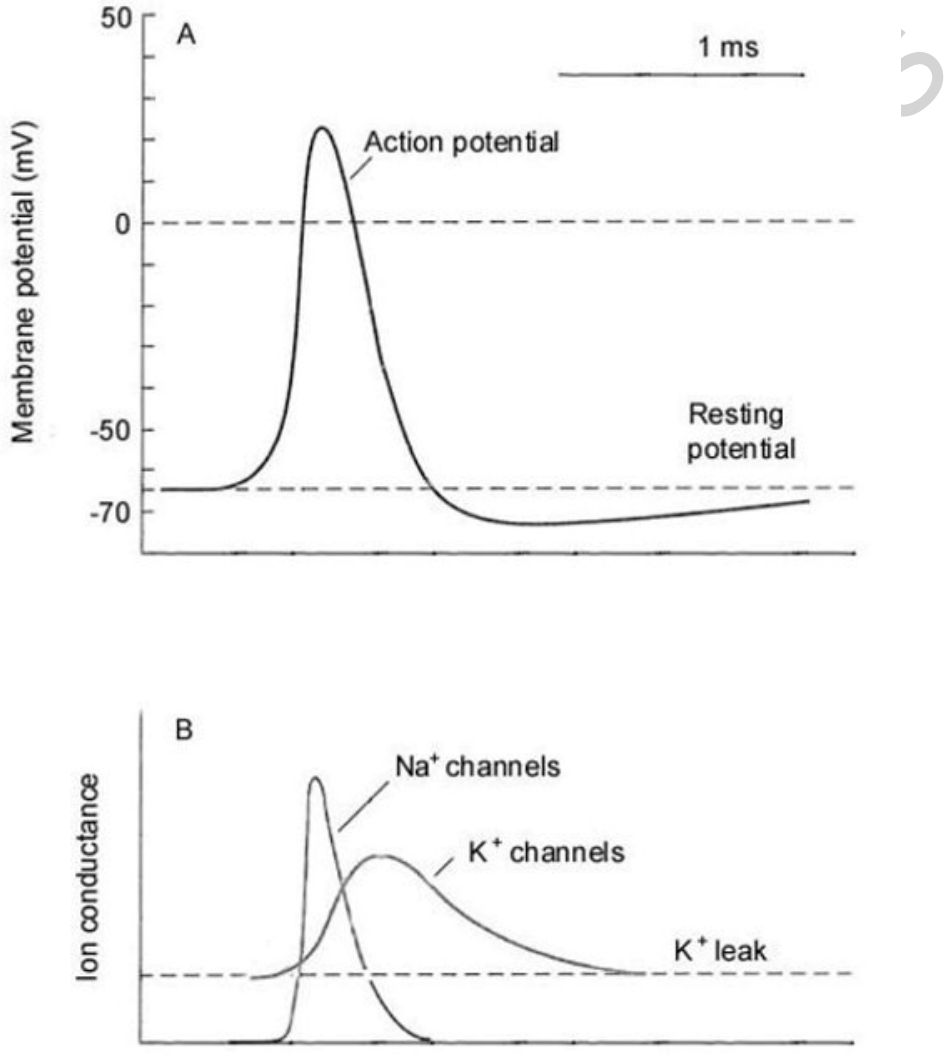

Figure 2. (A) Time course on an action potential showing the spike potential with the overshoot and after-hyperpolarization. (B) The changes in Na^+ and K^+ conductances underlying the action potential.

Notes: The rapid and transient increase in Na^+ permeability initiates the propagating action potential. The inactivation of voltage-dependent Na^+ channels and the delayed activation of K^+ channels cause repolarization and generate transient hyperpolarization.

-
-
-

Bibliography

Bear M.F., Connors B.W., and Paradiso M.A. (2001). Chapter 2: Neurons and glia; Chapter 3: The neuronal membrane at rest; Chapter 4: The action potential; Chapter 5: Synaptic transmission. *Neuroscience. Exploring the Brain, Second Edition*, pp. 23–130. Philadelphia: Lippincott Williams & Wilkins. [Concise and easy-to-read texts on the essentials of nerve cells, membrane potentials, and synaptic functions.]

Clemens J.D. (1996). Transmitter time course in the synaptic cleft: its role in central synaptic function. *Trends in Neuroscience* **19**, 163–171. [An analysis of the kinetics of neurotransmitter actions at chemical synapses.]

Fagni L., Chavis P., Ango F., and Bockaert J. (2000). Complex interactions between mGluRs, intracellular Ca^{2+} stores and ion channels in neurons. *Trends in Neuroscience* **23**, 80–88. [A review of the Ca^{2+} fluxes and concentrations and the synaptic metabotropic glutamate receptors.]

Kandel E.R., Schwartz J.H., and Jessell T.M. (ed.) (2000). Chapter 2: Nerve cells and behavior (by E.R. Kandel); Chapter 4: The cytology of neurons (by J.H. Schwartz and G.L. Westbrook); and Chapter 7: Membrane potential; Chapter 8: Local signaling: passive electrical properties of the neuron; and Chapter 9: Propagated signaling: the action potential (by J. Koester and S.A. Siegelbaum). *Principles of Neural Science, Fourth Edition*, pp. 67–87 and 125–174. New York: McGraw-Hill. [These chapters give a sophisticated overview of the structures of nerve cells, glial cells, and synapses in the nervous system. The eletrochemical events associated with the genesis of action potentials and signal transmission at nerve endings are characterized in a thorough manner.]

Parnas H., Segel L, Dudel J., and Parnas I. (2000). Autoreceptors, membrane potential and the regulation of transmitter release. *Trends in Neuroscience* **23**, 60–68. [A critical evaluation of the interactions of autoreceptors, Ca^{2+}, and neurotransmitter release.]

Piccolino M. and Pignatelli A. (1996). Calcium-independent synaptic transmission: artifact or fact? *Trends in Neuroscience* **19**, 120–125. [Does calcium-independent synaptic transmitter release occur or not?]

Sah P. (1996). Ca^{2+}-activated K^{+} currents in neurons: types, physiological roles and modulation. *Trends in Neuroscience* **19**, 150–154. [A short review on the role of potassium channels in synaptic transmission.]

Siegel G.J., Agranoff B.W., Albers R.W., Fisher S.K., and Uhler M.D. (eds.) (1999). Chapter 6: Electrical excitability and ion channels (by B. Hille and W.A. Catterall); Chapter 20: G proteins (by E.J. Nestler and R.S. Duman); Chapter 21: Phosphoinosidites (by S.K. Fischer and B.W. Agranoff); Chapter 22: Cyclic nucleotides (by R.S. Duman and E.J. Nestler); and Chapter 23: Calcium (by J.W. Putney Jr.). *Basic Neurochemistry: Molecular, Cellular and Medical Aspects, Sixth Edition*, pp. 119–138, 401–414, 415–432, 433–452, 453–470. Philadelphia and New York: Lippincott-Raven. [These book chapters describe in detail the roles of ion channels in impulse generation and signal transmission and the functions of intracellular signaling mechanisms.]

Biographical Sketches

Simo S. Oja is Professor in Biomedical Sciences (physiology), University of Tampere, Director of the Tampere Brain Research Center, and Docent in Biochemistry, University of Oulu, Finland. He was born in 1939 in Kärkölä, Finland. He obtained his Master of Science (M.Sc.) in 1962; Medical Doctor (M.D.) in 1964; Licentiate in Philosophy (Ph.L.) in 1965; Doctor of Philosophy (Ph.D.) in 1966; Doctor of Medical Sciences (M.Sc.D.) in 1967 (all at the University of Helsinki); and Master of Civil and Criminal Law (M.L.) in 1988 (University of Turku).

His academic appointments have included: Research Associate in Biochemistry, 1960 (University of Helsinki); Research Associate in Physiology, 1961–1963 (University of Helsinki); Postdoctoral Fellow in Physiology and Biophysics, 1963 (University of Kentucky, USA); Research Associate and Junior Research Fellow, 1964–1966 (Academy of Finland, Medical Research Council); Associate Professor in Biochemistry, 1966–1971 (University of Oulu); Senior Research Fellow, 1971–1972 (Academy of Finland, Research Council for Sciences); Docent in Biochemistry, 1971–present (University of Oulu); Professor in Biomedical Sciences (Medical Biochemistry), 1972 (University of Tampere); Professor in Biomedical Sciences (Physiology), 1973–present (University of Tampere); and Director of Brain Research Center, 1990–present (University of Tampere).

He is an editorial board member *Neurochemistry International*, 1982–1988, and editor *Neurochemical Research*, 1987–1998. Found qualified and competent for many professorial posts in Physiology, Biochemistry, Medical Chemistry, Medical Biochemistry, Dentistry Biochemistry, Pharmacology, Biophysics, and Zoology in several Finnish universities. He has participated in more than 150 international scientific congresses, meetings, and symposia since 1961, and has produced about 350 original scientific publications on different topics of physiology, biochemistry, and pharmacology, the majority of them on brain synaptic transmitters.

Pirjo Saransaari is Professor in Physiology, University of Tampere, Finland. He was born in 1944 in Tampere, Finland. He achieved his M.Sc. in 1967 (University of Helsinki) and his Ph.D. in 1980 (University of Oulu). His academic appointments include: Docent in Neurochemistry, 1981 (University of Tampere) and Docent in Physiology, 1986 (University of Tampere). Assistant and Senior Assistant in Biomedical Sciences, 1972–1982; Research Associate, Junior Research Fellow, and Senior Research Fellow, 1977–1987 (Academy of Finland, Medical Research Council); Senior Assistant in Physiology, 1983–1995 (University of Tampere); Associate Professor in Physiology 1996–1997 (University of Tampere); Professor in Medical Biochemistry, 1997–1998 (University of Tampere); Senior Scientist, 1992–1993 and 1999–1999 (Academy of Finland, Councils of Natural Sciences and Health Science); and Professor in Physiology, 1999–present (University of Tampere).

He has been Vice President of Finnish Physiologists' Association since 1996. He was a Member of the Executive Committee of the Finnish Brain Research Society from 1984 to 1992, and again from 1998 to the present. Found qualified and competent for many professorial posts in Physiology, Pharmacology, Biochemistry, and Medical Chemistry in several Finnish universities. Editor *Neurochemical Research*, 1999–present. Has participated in more than 100 international meetings, congresses, and symposia in physiology, pharmacology, biochemistry, and neurosciences since 1974. Has produced about 250 original scientific publications on chemistry, physiology, and pharmacology of brain neurotransmitters.