

# Nervous System, Immune System, and Cell Signaling

## INTRODUCTION

In the earlier chapters, description of the characteristic features of cell and its metabolism, division, homeostasis, etc were provided. Further, the process of protein synthesis and the role of enzymes in various cellular processes were explained. In this chapter, an insight into two systems, nervous system and immune system, which are critical to the maintenance of various organ systems in the body including the preservation of homeostasis, will be provided. This is achieved through several factors including proteinaceous chemicals produced by these two systems, neurotransmitter, hormones, cytokines and antibodies. Also, the importance of signaling between the cells in order to carry out the messages received from within and outside the body to manage the functions of the body such as metabolism and homeostasis is elucidated.

Nervous system in association with the endocrine system and immune system is important for the maintenance of homeostasis as explained in chapter 1. Nervous system and the endocrine system secrete various neurotransmitters, neuropeptides, hormones, growth factors, etc. These factors act as transducing agents to facilitate actions on behalf of the body in response to external signals received from the environment. For e.g., exam stress induces production of epinephrine, a neurotransmitter, by the nervous system and cortisol, a hormone, from the endocrine gland, adrenal gland, to prepare a student for the exam by raising the alertness level, lack of sleep, appetite, etc. Meanwhile, the immune system through the production of cytokines, antibodies, and other immune molecules helps the body to fight against any invading microorganisms and foreign objects. All the three systems work together to achieve homeostasis so that the organism survives, reproduces, and propagates its kind in the universe. This is accomplished through the process of cell signaling through a

variety of methods. The products of the systems, neurotransmitters, neuropeptides, hormones, antibodies, and cytokines bind to the receptors on the surface of the cells to bring about changes within the cytoplasm and nucleus to respond to the substance that is bound to its receptor and initiate appropriate synthesis of proteins to facilitate cell signaling.

## 5.1 NERVOUS SYSTEM

Human beings are unique in that we are able explore the depths of ocean to sending machines to the sky to observe the distant universe. This ability is made possible by the nervous system that is capable of coordinating the mental processes by which we perceive, act, learn and remember. The human brain is a network of billions of individual nerve cells interconnected in systems that construct our perceptions of the external world, fix our attention, and control the machinery of our actions. Our brain is compared to a supercomputer that is yet to be invented.

### History of neuroscience

Human beings were interested in the concept of 'mind' and its structural localization in the body from time immemorial. Some of the earlier concepts from Sumerian and Mesopotamian records (4000 BC) on the euphoric effects of drugs and Chinese reports (2700 BC) on acupuncture demonstrated role of nervous system on bodily functions. Edwin Smith Surgical papyrus (1700 BC) from Egypt first described the presence of brain and its anatomy including the presence of cerebrospinal fluid. The following table gives a brief history of the events in neuroscience:

**Table 5.1 History of neuroscience**

460-400 B. C.	Hippocrates mentions epilepsy is due to brain disorder and declares that the seat of intelligence resides in the brain
129-200 A. D.	Galen delivers a lecture on the importance of brain in regulating body
1452-1519	Leonardo da Vinci demonstrates the anatomy of ventricles in the brain through a wax cast
1514-1564	Andreas Vesalius publishes books on anatomy and physiology of human body. Also, discusses the importance of pineal gland and corpus striatum in the brain
1852-1934	Santiago Ramon y Cajal hypothesized that the <u>nervous system</u> is made up of several neuronal cells and demonstrates the presence of astrocytes, a type of glial cells.
1857-1952	Charles Sherrington explained synapse, reflex, and functions of neurons

1952	Hodgkin and Huxley demonstrated the quantitative model of action potential
2000	Arvid Carlsson, Paul Greengard and Eric Kandel share the Nobel Prize for their discoveries concerning signal transduction in the nervous system

The complex nature of the brain and associated nervous system allow the human beings to perform activities that are far superior to other animals. It also regulates a range of bodily functions from heart rate, emotions, learning, memory, sexual functions, and also, influences the immune system to maintain the healthy status of individuals. The highly sophisticated neural machine, the brain, gets continuous stream of information from the surrounding environment and organizes them into perceptions translating them into appropriate behavioral responses. All of this is accomplished by the brain using nerve cells and the connections between them.

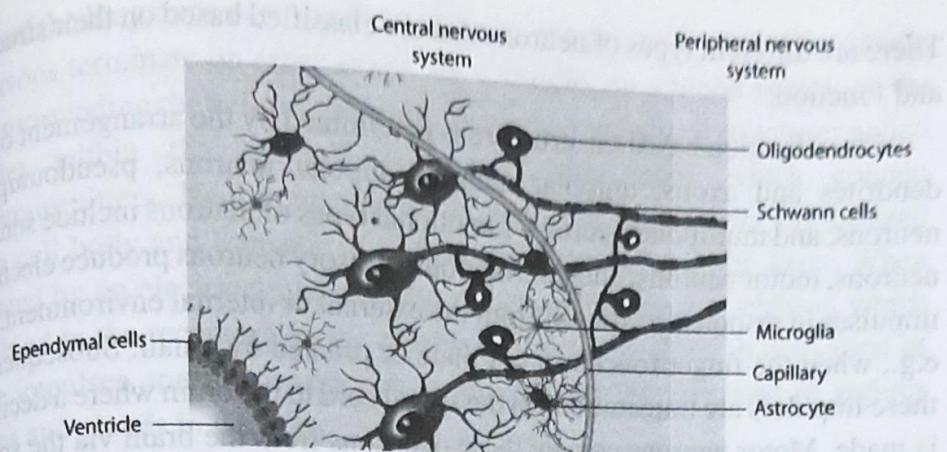
Individual nerve cells, the basic units of the brain, are relatively simple in their morphology and share the same basic architecture. The nervous system has two classes of cells: *glial cells (glia)* and *nerve cells (neurons)*.

## Glial cells

Glial cells play a supporting role in the nervous system. They are more in number compared to the neurons and in fact, outnumber the neurons by about 10 to 1 in the brain and make up half of the brain's volume. Another characteristic feature of glial cells is that they can be replaced throughout life unlike neurons which cannot be restored once they die. In general, glial cells do not transmit/conduct electrical impulses like the neurons. The name for these cells derives from the Greek word for glue. In actual terms, the glia do not commonly hold nerve cells together but surround the neurons. There are four main types of glial cells: **astrocytes**; myelin-producing **oligodendrocytes** and **Schwann cells**; **ependymal cells**; and **microglia** (Fig. 5.1).

## Types of glial cells

**Astrocytes:** These are the most abundant glial cell type and have star-shaped structure. Astrocytes are found surrounding the neurons providing them structural support so that the neurons are held in place. Through their contacts with the nearby blood vessels, they provide nourishment in the form of glucose and other nutrients to the neurons. In addition, they reuptake neurotransmitters from the synapse, control the ion ( $K^+$ ,  $Ca^{2+}$ ) concentrations in the extracellular area, synthesize and release growth factors and other molecules for neuronal growth and maintenance, and remove any dead cells in case of an injury or neuronal death.



**Fig. 5.1** Different types of glial cells in the central and peripheral nervous systems.

**Oligodendrocytes:** These glial cells are found in the brain and spinal cord (central nervous system) while they are referred to as *Schwann cells in the peripheral nervous system*. Both the cell types do not have long extensions like the astrocytes and their main function is to form myelin sheaths around the myelinated axons. Also, they are involved in providing nutritional support and Schwann cells help in the repair of damaged neurons outside the central nervous system. Myelin is the covering of the glial extensions that wrap around the axon of a neuron in many layers. Myelinated neurons have extra electrical insulation that facilitates the nerve signals to travel faster and reach farthest areas in the body.

**Ependymal cells:** These cells surround the ventricles which are fluid-filled spaces within the brain. They do not possess any cellular processes from the cells. Their major role is to secrete cerebrospinal fluid (CSF) that circulates within the ventricles and spinal canal enclosing the spinal cord. The function of the CSF is to protect the brain from any shocks to the brain in case any trauma/blows to the head and bathes the brain and the spinal cord. It also serves as a vehicle for eliminating waste products from the brain.

**Microglia:** These are small cells, least abundant, and belong to the immune system. They originate from monocytes and circulate within the brain. They remove dead neurons, neuronal debris, and microorganisms through "phagocytosis." Microglial cells also produce immune molecules and growth factors that aid the damaged neurons to recover from injury.

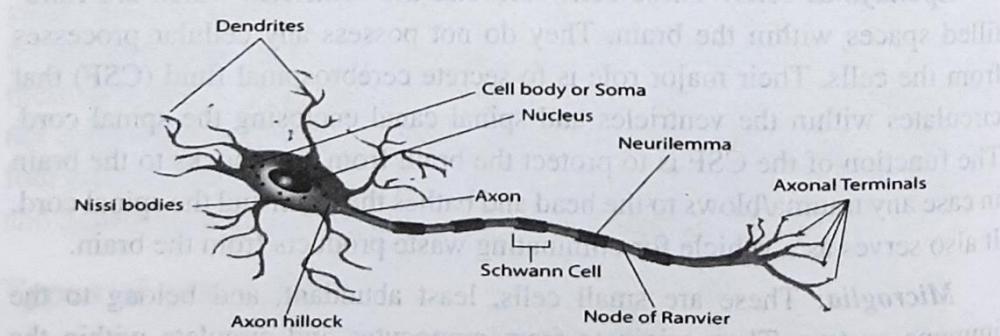
### Nerve cells - Neurons

The basic structural unit of the nervous system is the "neuron." It is the signaling unit that transmits electrical impulses across billions of neurons within the brain and the spinal cord reaching out to every area of the body.

There are different types of neurons that are classified based on their structure and function.

Classification based on structure is determined by the arrangement of the dendrites and axons: unipolar neurons, bipolar neurons, pseudounipolar neurons, and multipolar neurons. Functional types of neurons include sensory neurons, motor neurons, and interneurons. Sensory neurons produce electrical impulses in response to stimuli from the external or internal environment. For e.g., when the finger touches a hot plate or pricked by a nail. Subsequently, these impulses are transmitted via the spinal cord to the brain where a decision is made. Motor neurons convey these decisions from the brain via the spinal cord to the muscles or glands. For e.g., withdrawal of the finger or hand from the hot plate or nail involving the movement of muscles or secretions of fluids in the case of glands. This circuitry is also called as “**reflex action**.” Interneurons are in between two neurons facilitating transmission of signals between these two.

Neurons have a **cell body or soma**, multiple projects from the cell body called **dendrites**, and a single **axon** (Fig. 5.2). The **cell body** has an outer plasma membrane that encloses the cytoplasm containing the nucleus and a number of organelles. As described in chapter 1, the nucleus is the command center of the cell regulating the activities of other organelles. Neurons do not divide or reproduce like other cells and are capable of generating electrochemical signals unlike other cells.



**Fig. 5.2** A neuron showing a cell body with dendrites and axons.

From the irregularly shaped cell body of the neuron, a number of processes extend towards neighboring neurons. They branch like a tree and are referred to as “**dendritic tree**.” Dendrites receive messages from the surrounding neuronal structures and move them towards the cell body for further processing and transmission. Another key feature of the neuron is the presence of a single **axon** that carries the messages away from the cell body.

Some of the long axons are myelinated due to the presence of myelin sheath. The axons terminate on other axons, on a muscle, on a blood vessel, or the fluid surrounding the cells of the body. There are specialized structures called neurotransmitters. Neurotransmitters are chemical messengers synthesized in the cell body and transported to the axon terminals via the axon. When activated by an electrical impulse, the neurotransmitters are released which then bind to the receptors on the neighboring cells resulting in activation of nerve impulses, muscle contraction, or modulating the functions of various organs and glands in the body.

**Synapse:** The tiny gap between two adjoining neurons measures about 10 to 20 nanometers is called the synaptic cleft (Fig. 5.3). Synapse refers to the synaptic cleft and the areas on the two adjoining neurons that are involved in sending out (presynaptic) the signal and reception (postsynaptic) of the chemical signal. The presynaptic neuron sends out the message by releasing neurotransmitters into the synaptic cleft. Every neuron is capable of synthesizing one or more types of neurotransmitters and stores them in synaptic vesicles. When the nerve signal arrives at the axon terminal, the synaptic vesicle fuses to the presynaptic membrane and empties the content into the synaptic cleft. These chemical messengers diffuse across the synaptic cleft and binds to a specific receptor on the postsynaptic neuron. *This binding is similar to "lock and key" process observed between enzyme and substrate binding.*

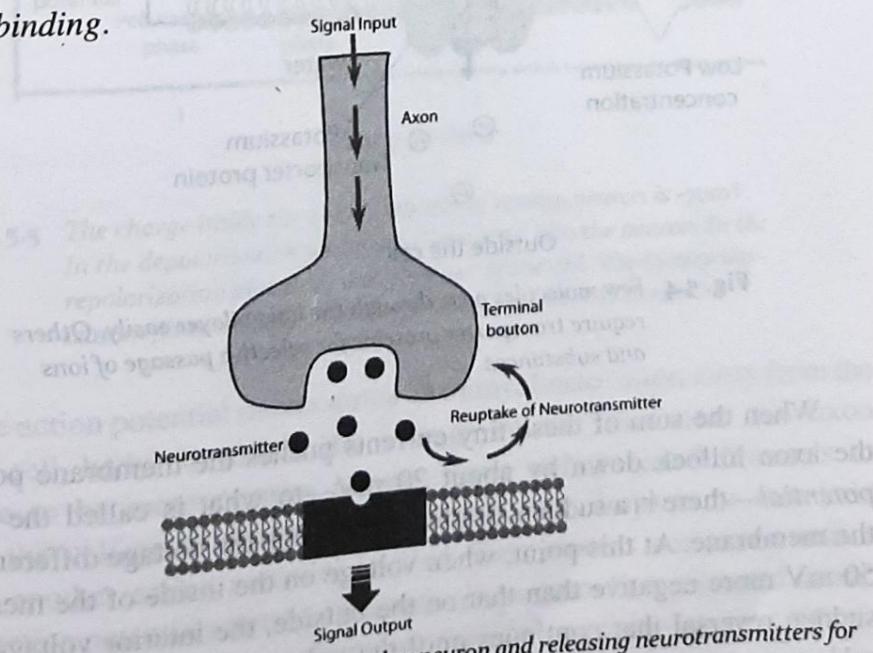
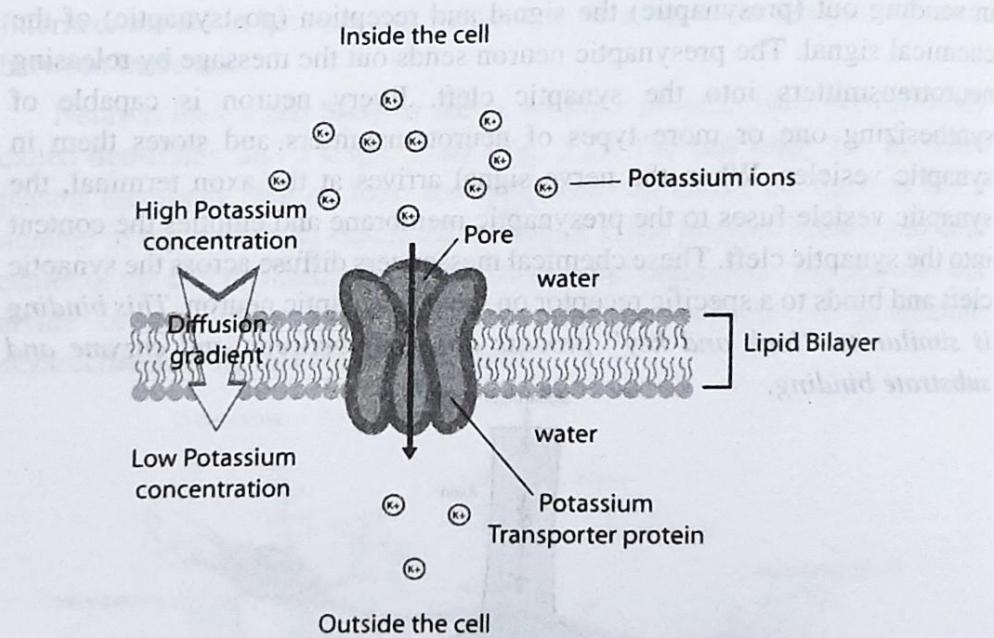


Fig. 5.3 A neuron forming a synapse with another neuron and releasing neurotransmitters for propagation of action potentials and thus, influencing various functions.

## Action Potential

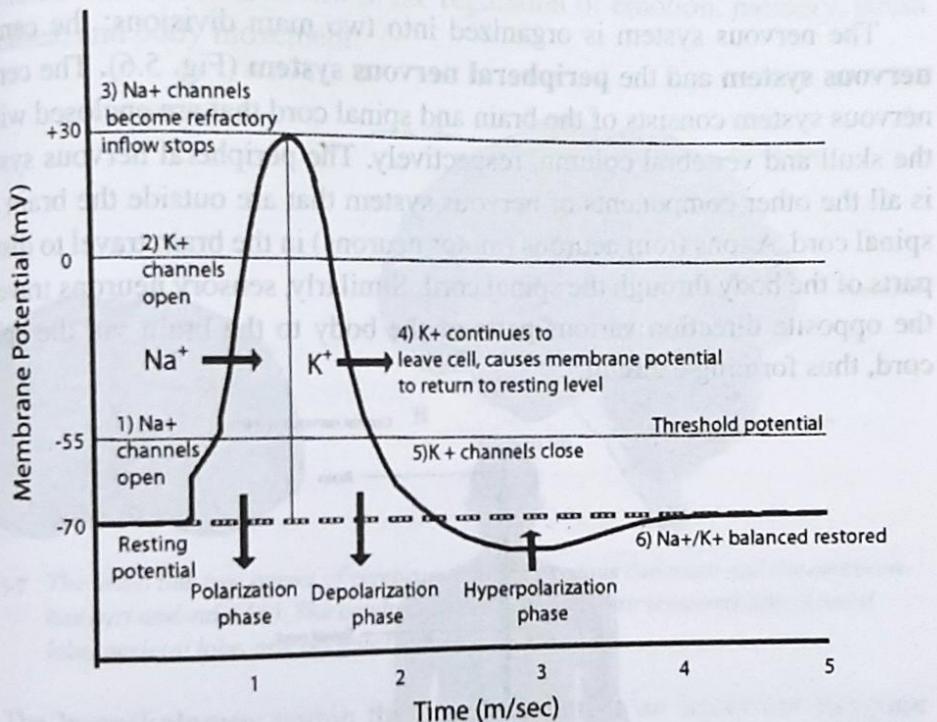
The unique feature of the neurons is its capability to generate an electrical current in response to excitation is called **action potential**. As sodium ion on the outside of the cell enter the postsynaptic neuron through ion channels activated by neurotransmitters, small electrical currents are produced (Fig. 5.4). These then travel to the **axon hillock**, the junction between the cell body and the axon, where the summation of all the electrical currents occur. Some of the neuronal signals are excitatory which open  $\text{Na}^+$  channels while others are inhibitory that open  $\text{Cl}^-$  or  $\text{K}^+$  channels.. Depending on the strength of these signals, the axon hillock decides either to propagate or not to propagate an action potential. It will only fire an action potential only if there are enough currents to open a large enough number of voltage-gated  $\text{Na}^+$  channel to make the membrane over the axon hillock reach its **threshold potential**.



**Fig. 5.4** Few molecules pass through the lipid bilayer easily. Others require transporter proteins for selective passage of ions and substances

When the sum of these tiny currents pushes the membrane potential of the axon hillock down by about 20 mV—to what is called the *threshold potential*—there is a sudden, dramatic change in the voltage difference across the membrane. At this point, when voltage on the inside of the membrane is 50 mV more negative than that on the outside, the interior voltage makes a sudden reversal that continues until the voltage inside the membrane is 30 mV more *positive* than that outside the membrane. This sudden change in

voltage is the **action potential** (Fig. 5.5). It lasts for about 1 millisecond. There is a sudden influx of  $\text{Na}^+$  ions while there is an efflux of  $\text{K}^+$  ions leading to a slightly more negative than the resting potential. The drop in voltage below that of the resting potential is called **hyperpolarization**. As  $\text{K}^+$  ions begin to reenter the cell, the voltage inside the membrane slowly returns to the resting potential. The reason that the action potential travels in only one direction down the axon is because there is a **refractory period** that begins immediately after the firing of an action potential.



**Fig. 5.5** The charge inside the cell membrane of resting neuron is  $-70\text{mV}$ . In the depolarization phase,  $\text{Na}^+$  ions pour into the neuron. In the repolarization phase,  $\text{K}^+$  ions flow out of the cell. The hyperpolarization phase is due to the excess of  $\text{K}^+$  ions leaving the cell.

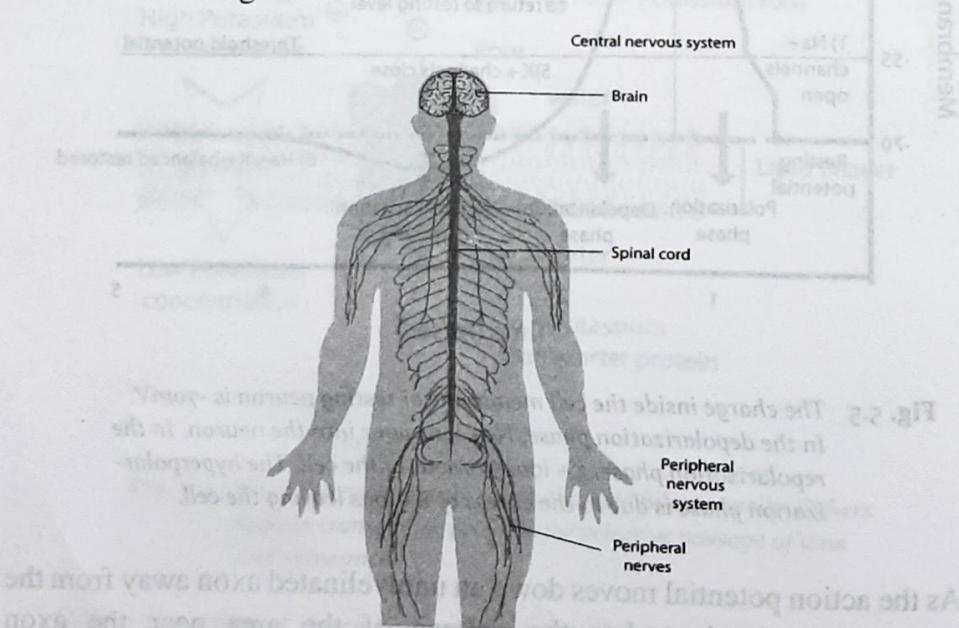
As the action potential moves down an unmyelinated axon away from the neuronal cell body, it makes the voltage of the area near the axon membrane to be more positive causing more voltage-gated channels to open. As the voltage of the intracellular membrane drops to its threshold potential, another action potential is fired. This process continues until a series of action potentials travels the length of the axon. In myelinated axons, the extra insulation lets nerve impulses travel very fast—up to 120 m/s (394 feet/s).

## 5.2 ORGANIZATION OF THE NERVOUS SYSTEM

### Neural networks in the human beings

Human nervous system is such a complex system that none of the computers have been able to match its speed and processing power. Without us being aware, several important functions are regulated by the nervous system which enable us to respond to the surrounding environment and maintain homeostasis.

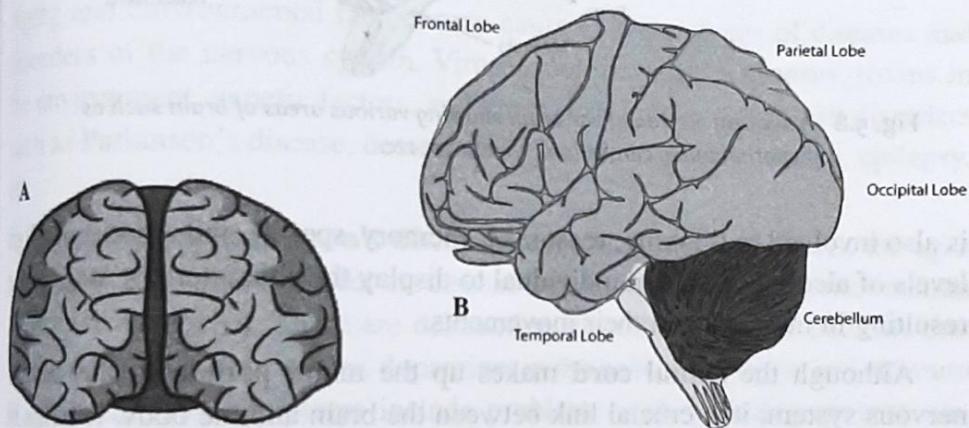
The nervous system is organized into two main divisions: the **central nervous system** and the **peripheral nervous system** (Fig. 5.6). The central nervous system consists of the brain and spinal cord that are enclosed within the skull and vertebral column, respectively. The peripheral nervous system is all the other components of nervous system that are outside the brain and spinal cord. Axons from neurons (motor neurons) in the brain travel to distant parts of the body through the spinal cord. Similarly, sensory neurons travel in the opposite direction various parts of the body to the brain via the spinal cord, thus forming a circuit.



**Fig. 5.6** Nervous system is organized into central nervous system (brain and spinal cord) and the peripheral nervous system (cranial nerves and peripheral nerves).

**The Central Nervous System:** The major components in the brain are cerebrum, diencephalon, cerebellum, and the brain stem. In addition, the spinal cord extends as a projection of the brain stem into the vertebral column.

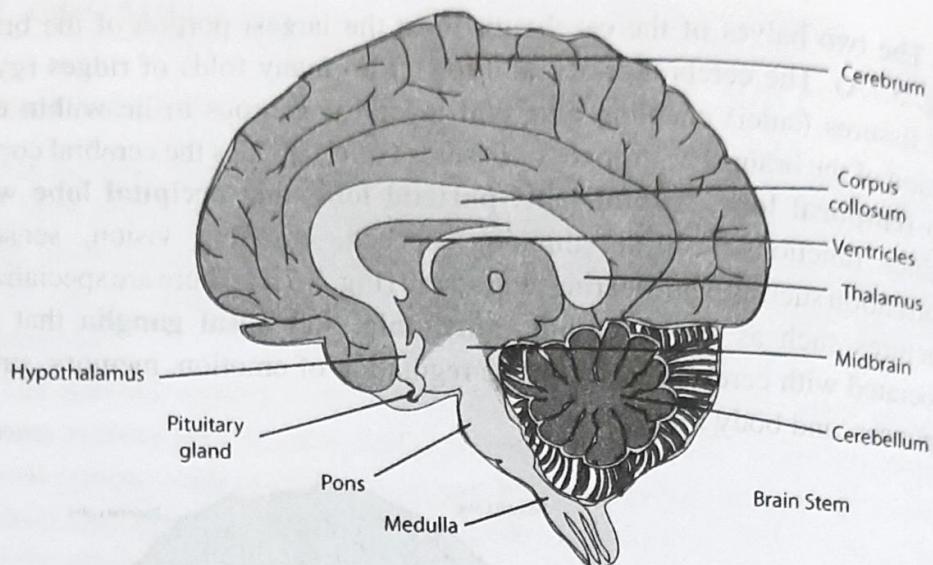
The two halves of the **cerebrum** form the largest portion of the brain (Fig. 5.7A). The cerebral cortex is thrown into many folds of ridges (gyri) and fissures (sulci) enabling several layers of neurons to lie within this portion of the brain. The grooves or fissures (sulci) divides the cerebral cortex into **temporal lobe**, **frontal lobe**, **parietal lobe**, and **occipital lobe** with distinct functions such as thinking, speech, emotion, vision, sensory information such as pain, hearing, and sound (Fig. 5.7B). There are specialized structures such as **hippocampus**, **amygdala**, and **basal ganglia** that are associated with cerebral cortex in the regulation of emotion, memory, stress responses, and body movement.



**Fig. 5.7** The brain has two halves of cerebrum joined by corpus callosum and the cerebrum has gyri and sulci (A). The cerebral cortex is divided into temporal lobe, frontal lobe, parietal lobe, and occipital lobe (B).

The **hypothalamus** within the **diencephalon** is an important structure that control various crucial body functions such as reproduction, regulation of body temperature, biological rhythms, metabolism and growth, stress responses, immune system, etc (Fig. 5.8). These are mediated through the release of hormones which then act on the **pituitary gland** below it. The hormones released from the pituitary acts on the target **endocrine glands** to govern body functions. This is done in concert with the autonomic nervous system. Together, hypothalamus, pituitary, and the target endocrine glands form the **neuroendocrine system**.

The **brain stem** consists of **pons** and **medulla oblongata** that are important for cardiovascular and respiratory functions, sleep, consciousness, and alertness. The **cerebellum** is below the occipital lobe of the cerebral cortex and performs critical functions such as coordination of movements, maintenance of posture, and the learning of motor skills. It is believed that it



**Fig. 5.8** A sagittal section of the brain showing various areas of brain such as hypothalamus, cerebellum, thalamus, etc.

is also involved in thinking, reasoning, memory, speech, and emotions. High levels of alcohol causes an individual to display the characteristic staggering resulting in imbalance in their movements.

Although the **spinal cord** makes up the minor portion of the central nervous system, it is crucial link between the brain and the body. It helps in relaying information from the periphery (sensory input) to the brain and carrying commands from the brain (motor output) to the peripheral parts of the body.

**The Peripheral Nervous System:** The 10 pairs of cranial nerves that come out of the brain and the nerves that exit the spinal cord constitute the peripheral nervous system. Sensory neurons and their axons, as well as the axons of motor neurons in the spinal cord and preganglionic neurons located in the central nervous system, are all part of the peripheral nervous system. It is divided into two major subdivisions, the **somatic nervous system** and the **autonomic nervous system**. The somatic nervous system includes sensory neurons and sensory and motor nerves of voluntary muscles that control voluntary muscle movements.

The autonomic nervous system is divided into the **sympathetic nervous system (SNS)** and the **parasympathetic nervous system**. The SNS plays a major role in the “flight or fight” response during which the body is prepared to either run away or resist the danger. The parasympathetic nervous system exerts a maintenance control especially following a sympathetic nervous system response.

Several neurochemicals, **neurotransmitters** and **neuropeptides**, mediate the effects of the central and peripheral nervous systems. Acetylcholine was the first neurotransmitter discovered. It plays a major role in thinking, memory, arousal, and movement. Neurotransmitters belonging to the class of monoamines include dopamine, norepinephrine, epinephrine, and serotonin have a wide variety of functions in the body. Endogenous opioids are neuropeptides responsible for analgesia (pain relief), euphoria (a feeling of extreme joy or elation)

### **5.3 DISEASES OF THE NERVOUS SYSTEM**

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Aging and environmental factors may cause different types of diseases and disorders of the nervous system. Viruses, autoimmune responses, toxins in the environment, genetic factors, and drugs may induce movement disorders such as Parkinson's disease, dementia, Alzheimer's disease, stroke, epilepsy, etc.

The onset of **Parkinson's disease** is usually observed between the ages of 50 to 60. The exact cause for the disease is unknown although environmental toxins are suspected. There are destruction of cell bodies and neurons that produce the neurotransmitter, dopamine, in the substantia nigra and striatum of the brain. The symptoms include problems with initiating movements, slowness in movement, rigidity due to increased muscle tone, and tremors of the hands, arms, and head.

**Dementia** is another disorder associated with aging seen in patients over the age of 60. Changes in brain tissues lead to loss of cognitive and behavioral functions resulting in loss of memory, inability to learn new tasks, irritation, etc. **Alzheimer's disease** is the most common form of dementia observed in elderly. It is more prevalent in Western countries but with increase in the elderly population in India, there will be an increase in its incidence here too in the near future. It is the most common form of dementia characterized by loss of memory and other cognitive problems. As the disease progresses, there are other symptoms such as mood swings, language problems, poor judgment, confusion, and changes in personality. There is severe loss of neurons in the cortex and also, hippocampus and other limbic regions of the temporal lobe. The brain tissue shows deposition of amyloid plaques containing b-amyloid protein and neurofibrillary tangles due to accumulation of tau protein that is present in the microtubules (cytoskeleton).

## 5.4 COMPUTER-BASED NEURAL NETWORKS

The brain's network of neurons forms a massively parallel information processing system. This contrasts with conventional computers, in which a single processor executes a single series of instructions.

Against this, consider the time taken for each elementary operation: neurons typically operate at a maximum rate of about 100 Hz, while a conventional CPU carries out several hundred million machine level operations per second. Despite of being built with very slow hardware, the brain has quite remarkable capabilities:

- its performance tends to degrade gracefully under partial damage. In contrast, most programs and engineered systems are brittle: if you remove some arbitrary parts, very likely the whole will cease to function.
- it can learn (reorganize itself) from experience.
- this means that partial recovery from damage is possible if healthy units can learn to take over the functions previously carried out by the damaged areas.
- it performs massively parallel computations extremely efficiently. For example, complex visual perception occurs within less than 100 ms, that is, 10 processing steps!
- it supports our intelligence and self-awareness through yet to be determined mechanism.

As a discipline of Artificial Intelligence, Neural Networks attempt to bring computers a little closer to the brain's capabilities by imitating certain aspects of information processing in the brain, in a highly simplified way.

The neurons in "Neural Network" are not biological. They are extremely simple abstractions of biological neurons, realized as elements in a program or perhaps as circuits made of silicon. Networks of these artificial neurons do not have a fraction of the power of the human brain, but they can be trained to perform useful functions.

Two new concepts were most responsible for the rebirth of neural networks. The first was the use of statistical mechanics to explain the operation of a certain class of recurrent network, which could be used as an associative memory. The second key development of the 1980s was the back-propagation algorithm for training multilayer perceptron networks, which was discovered independently by several different researchers. These new developments reinvigorated the field of neural networks. In the last few years,

thousands of papers have been written, and neural networks have found many applications. The field is vibrant with new theoretical and practical work.

Neural networks have been applied in many fields and a partial list of its applications are provided below:

**Aerospace:** Aircraft autopilots, flight path simulations, aircraft control systems, autopilot enhancements, aircraft component simulations, aircraft component fault detectors

**Automotive:** Automatic guidance systems in vehicles, warranty activity analyzers

**Banking:** Check and other document readers, credit application evaluators

**Cognitive science:** Modeling higher level reasoning, language, problem solving, Modeling lower level reasoning, vision, audition speech recognition, speech generation

**Defense:** Weapon steering, target tracking, object discrimination, facial recognition, new kinds of sensors, sonar, radar and image signal processing including data compression, feature extraction and noise suppression, signal/image identification

**Electronics:** Code sequence prediction, integrated circuit chip layout, process control, chip failure analysis, machine vision, voice synthesis, nonlinear modeling

**Entertainment:** Animation, special effects, market forecasting

**Financial:** Real estate appraisal, loan advisor, mortgage screening, corporate bond rating, credit line use analysis, portfolio trading program, corporate financial analysis, currency price prediction

**Insurance:** Policy application evaluation, product optimization

**Manufacturing:** Manufacturing process control, product design and analysis, process and machine diagnosis, real-time particle identification, visual quality inspection systems, beer testing, welding quality analysis, paper quality prediction, computer chip quality analysis, analysis of grinding operations, chemical product design analysis, machine maintenance analysis, project bidding, planning and management, dynamic modeling of chemical process systems

**Mathematics:** Nonparametric statistical analysis and regression.

**Medical:** Breast cancer cell analysis, EEG and ECG analysis, prosthesis design, optimization of transplant times, hospital expense reduction, hospital quality improvement, emergency room test advisement

**Neurobiology:** Modeling models of how the brain works, neuron-level, higher levels: vision, hearing, etc. Neural networks is especially helpful in the field of cognitive neuroscience.

**Oil and Gas:** Exploration

**Philosophy:** Can human souls/behavior be explained in terms of symbols, or does it require something lower level, like a neurally-based model?

**Robotics:** Trajectory control, forklift robot, manipulator controllers, vision systems

**Speech:** Speech recognition, speech compression, vowel classification, text to speech synthesis

**Securities:** Market analysis, automatic bond rating, stock trading advisory systems

**Telecommunications:** Image and data compression, automated information services, real-time translation of spoken language, customer payment processing systems

**Transportation:** Truck brake diagnosis systems, vehicle scheduling, routing systems

## 5.5 IMMUNE SYSTEM

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Immune system is crucial to the maintenance of healthy status of an organism by protecting it from microorganisms such as bacteria, virus, protozoans, etc. The origin of “Immunology” is usually attributed to **Edward Jenner** who discovered in 1796 that cowpox, or vaccinia, induced protection against human smallpox that often lead to death. This procedure discovered by Jenner was called as “vaccination.” Although Jenner’s bold experiment was successful, it took almost two centuries for smallpox vaccination to become universal. This procedure enabled the World Health Organization to announce in 1979 that smallpox had been eradicated making it the greatest triumph of modern medicine. Also, this technique was widely used to fight against several other bacterial and viral diseases such as polio.

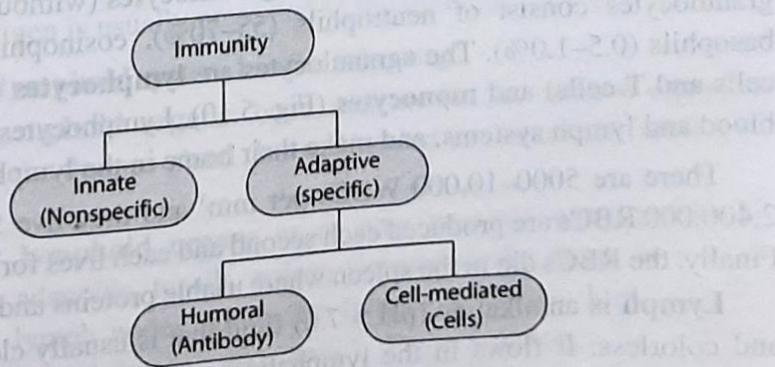
Late in the 19<sup>th</sup> century, **Robert Koch** proved that infectious diseases are caused by microorganisms, each one responsible for a particular disease. This led to the classification of disease-causing microorganisms into four broad categories; viruses, bacteria, pathogenic fungi, and parasites.

In the 1880s, **Louis Pasteur** devised a vaccine against cholera in chickens, and developed a rabies vaccine that proved to be a spectacular success upon

its first trial in a boy bitten by a rabid dog. In the early 1890s, **Emil von Behring** and **Shibasaburo Kitasato** discovered that the serum of animals immune to diphtheria or tetanus contained a specific "antitoxic activity"-later called **antibodies**-that could confer short-lived immunity on unimmunized individuals.

The immune system functions on the basic principle of distinguishing self from **non-self**. The body will not attack its own cells (**self**), a learning process that occurs early in life whereas it can attack "foreign (**non-self**)" to protect the organism against development of diseases. When this delicate balance is abolished, individuals develop **autoimmune diseases** such as diabetes type-I, multiple sclerosis, lupus, rheumatoid arthritis, etc. In autoimmune diseases, the cells of the immune system attack cells within the organism leading to impairment of functions rigidity of hands and legs in multiple sclerosis, high levels of glucose in diabetes type-I, etc. In certain cases, simple pollen grains, odor, etc are capable of making the immune system to produce an immune response. This is observed in the case of allergies and the simple substance that elicits the response is called an **allergen**.

A specific **immune response** such as the production of antibodies against a particular pathogen is known as an **adaptive immune response** because it occurs during the lifetime of an individual as a method to prevent further infection with that pathogen. In many cases, an adaptive immune response confers lifelong **protective immunity** to reinfection with the same pathogen. This is different from the other type of immune response especially, **innate immunity**. **Innate immunity** is conferred by all those elements with which an individual is born and that are always present and available at very short notice to protect the individual from challenges by foreign invaders (Fig.5.9).



**Fig. 5.9** Immune system responds to foreign organisms through innate immunity and adaptive immunity (humoral and cell-mediated immunity)

An **antigen** is any substance that elicits an immune response such as virus and bacteria. More specifically, any substance that is capable of generating antibody is called as an antigen.

**Table 5.2** Summarizes and compares some of the features of the innate and adaptive immune systems.

Property	Innate	Adaptive
<b>Characteristics</b>	Antigen nonspecific	Antigen specific
	Rapid response (minutes)	Slow response (days)
	No memory	Memory
<b>Immune components</b>	Natural barriers (e.g., skin)	Lymphocytes
	Phagocytes	Antigen-recognition molecules (B cell and T cell receptors)
	Soluble mediators (e.g., complement)	Secreted molecules (e.g., antibody)
	Pattern recognition molecules	

## Fluid systems of the body

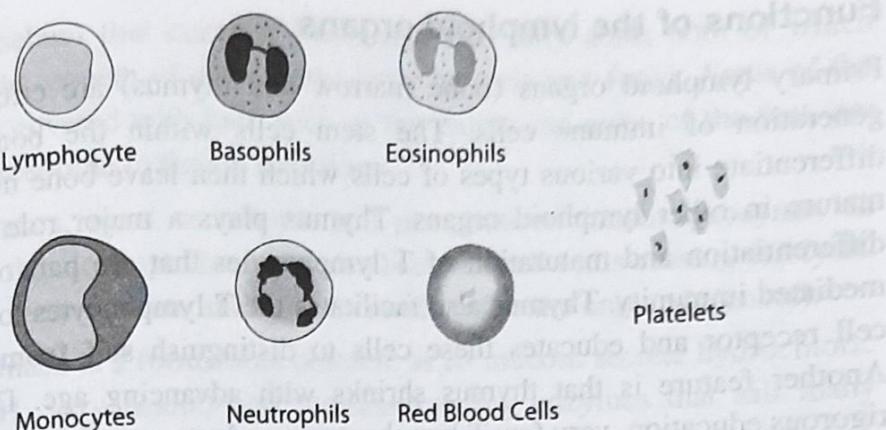
There are two main fluid systems in the body: **blood** and **lymph**. The blood and lymph systems are connected with each other throughout the body and they are responsible for transporting the cells of the immune system.

The cells in the blood originate from the stem cells in the bone marrow through a process called hematopoiesis (Fig. 5.8). As explained earlier in chapter 1 and 2, stem cells differentiate into various other types of blood cells such as **erythrocytes** (red blood cells or RBCs), **leukocytes** (white blood cells or WBCs), and **thrombocytes** (platelets).

The leukocytes are further subdivided into **granulocytes** (containing large granules in the cytoplasm) and **agranulocytes** (without granules). The granulocytes consist of neutrophils (55–70%), eosinophils (1–3%), and basophils (0.5–1.0%). The agranulocytes are **lymphocytes** (consisting of B cells and T cells) and **monocytes** (Fig. 5.10). Lymphocytes circulate in the blood and lymph systems, and make their home in the lymphoid organs.

There are 5000–10,000 WBCs per mm<sup>3</sup> and they live 5–9 days. About 2,400,000 RBCs are produced each second and each lives for about 120 days. Finally, the RBCs die in the spleen where usable proteins and iron are reused.

**Lymph** is an alkaline (pH > 7.0) fluid that is usually clear, transparent, and colorless. It flows in the lymphatic vessels and circulates among the cells, tissues, and organs ensuring that there is no invasion of foreign



**Fig. 5.10** Major cells in the blood: RBCs, platelets, granulocytes (neutrophils, eosinophils, and basophils) and agranulocytes (lymphocytes and monocytes).

substances. Lymphatic system does not contain RBCs but have only cells of the immune system. This special circulatory system for the immune cells is responsible for their two major functions, **diapedesis** and **chemotaxis**. In order to maintain the healthy status of an individual, it is important that the immune cells move to different parts of body quickly (diapedesis) and this movement of cells to a particular place is facilitated by chemical gradient (chemotaxis) in that area.

The lymph flows from the interstitial fluid through lymphatic vessels up to either the thoracic duct or right lymph duct, which terminate in the subclavian veins, where lymph is mixed into the blood. Lymph carries lipids and lipid-soluble vitamins absorbed from the gastrointestinal (GI) tract. Since there is no active pump in the lymph system, there is no back-pressure produced. The lymphatic vessels, like veins, have one-way valves that prevent backflow. Additionally, along these vessels there are small bean-shaped **lymph nodes** that serve as filters of the lymphatic fluid. It is in the lymph nodes where antigen is usually presented to the immune system.

The human **lymphoid system** has the following:

- **primary lymphoid organs:** bone marrow (in the hollow center of bones) and the thymus gland (located behind the breastbone above the heart), and
- **secondary lymphoid organs** at or near possible entry points for pathogens: adenoids, tonsils, spleen (located at the upper left of the abdomen), lymph nodes (along the lymphatic vessels located in the neck, armpits, abdomen, and groin), Peyer's patches (within the intestines).

## Functions of the lymphoid organs

Primary lymphoid organs (bone marrow and thymus) are critical to the generation of immune cells. The stem cells within the bone marrow differentiate into various types of cells which then leave bone marrow and mature in other lymphoid organs. Thymus plays a major role in further differentiation and maturation of T lymphocytes that are part of the cell-mediated immunity. Thymus also facilitates the T lymphocytes to acquire T cell receptor and educates these cells to distinguish **self from non-self**. Another feature is that thymus shrinks with advancing age. Due to the rigorous education, very few T lymphocytes graduate out of thymus.

The secondary lymphoid organs, spleen, lymph nodes and other lymphoid tissues, are important in capturing the antigens (foreign substances), production of antibodies, and induce T lymphocyte proliferation.

## 5.6 INNATE IMMUNITY

The innate immune system is the one that is present at the time of birth given to all from the mother. It is non-specific and attacks antigens equally without differentiating them. Since it is passed on through the mother, it is dependent upon the genetic makeup of the individual. Another key feature is that it does not possess "memory": it cannot remember the pathogen when it attacks again. The components of the innate immunity are surface barriers such as skin and mucous membranes, chemical factors such as saliva, tears, and fatty acids, and cells such as polymorphonuclear leukocytes, natural killer cells, dendritic cells, and macrophages.

### Surface barriers and Chemical factors

1. The first and, arguably, most important barrier is the **skin**. The skin cannot be penetrated by most organisms unless it already has an opening, such as a nick, scratch, or cut.
2. Mechanically, pathogens are expelled from the lungs by ciliary action as the tiny hairs move in an upward motion; coughing and sneezing abruptly eject both living and nonliving things from the respiratory system; the flushing action of tears, saliva, and urine also force out pathogens, as does the sloughing off of skin.
3. Sticky mucus in respiratory and gastrointestinal tracts traps many microorganisms.
4. Acid pH (<7.0) of skin secretions inhibits bacterial growth. Hair follicles

secrete sebum that contains lactic acid and fatty acids both of which inhibit the growth of some pathogenic bacteria and fungi. Areas of the skin not covered with hair, such as the palms and soles of the feet, are most susceptible to fungal infections.

5. Saliva, tears, nasal secretions, and perspiration contain **lysozyme**, an enzyme that destroys Gram-positive bacterial cell walls causing cell lysis. Vaginal secretions are also slightly acidic (after the onset of menses).
6. The stomach is a formidable obstacle as its mucosa secrete hydrochloric acid (pH: very acidic) and protein-digesting enzymes that kill many pathogens. The stomach can even destroy drugs and other chemicals.

### Cells of the innate immune system

**Polymorphonuclear (PMN) leukocytes** (granulocytes) include basophils, mast cells, eosinophils, and neutrophils. These cells have no mitochondria and get their energy from stored glycogen. They are non-dividing, short-lived (half-life of 6–8 hours, 1–4 day lifespan), and have a segmented nucleus. They live for short duration and contain enzyme-rich lysosomes within the cells. Once the foreign organisms are engulfed (phagocytosis), they are destroyed through these enzyme-rich lysosomes. In addition, they produce peroxide and superoxide radicals to cause destruction of the microorganisms. They constitute 50–75% of all leukocytes. The neutrophils provide the major defense against pyogenic (pus-forming) bacteria and are the first on the scene to fight infection. They are followed by the wandering macrophages about three to four hours later.

A **phagocyte** is a cell that attracts (by chemotaxis), adheres to, engulfs, and ingests foreign bodies. *Promonocytes* are made in the bone marrow, after which they are released into the blood and called circulating *monocytes*, which eventually mature into **macrophages** (meaning “big eaters”, see below).

Some *macrophages* are concentrated in the lungs, liver (Kupffer cells), lining of the lymph nodes and spleen, brain microglia, lung alveolar macrophages, synovial A cells, and osteoclasts. They are long-lived, depend on mitochondria for energy, and are best at attacking dead cells and pathogens capable of living within cells. Once a macrophage phagocytizes a cell, it places some of its proteins, called epitopes, on its surface. These surface markers serve as a danger signal to other immune cells that then recognized the form of the invader. All cells that do this are called **antigen-presenting cells (APCs)**.

**Dendritic cells** are long-lived cells that recognize antigens and pathogens for further phagocytosis. The morphological features of the cell resemble the dendrites of the nerve cell and hence, referred to as dendritic cell. They belong to the class of **APCs**. Langerhans cells, interstitial dendritic cells, interdigitating dendritic cells, and circulating dendritic cells are some of the types of dendritic cells. Among them, **Langerhans cells** found in the epidermis is one of the most efficient antigen-presenting cells. Once they come into contact with a foreign substance, they mature and activate other types of cells especially, T lymphocytes. Similar to macrophages, dendritic cells play an important role in both innate immunity and adaptive immunity.

**Natural killer cells** move in the blood and lymph to lyse (cause to burst) cancer cells and virus-infected body cells. They are large granular lymphocytes that attach to the glycoproteins on the surfaces of infected cells and kill them. Killing of foreign bodies are achieved by various cytotoxic molecules. One set of molecules causes pores in the membrane of the target cell while another set of molecules enter the target cell cause death of the cell.

**Eosinophils** are attracted to cells coated with complement, where they release major basic protein (MBP), cationic protein, perforins, and oxygen metabolites, all of which work together to burn holes in cells and helminths (worms). About 13% of the WBCs are eosinophils. Their lifespan is about 8–12 days. Neutrophils, eosinophils, and macrophages are all phagocytes.

The **complement system** is another key component of the innate immune system that facilitates the destruction of foreign bodies. It coats microbes with molecules that make them more susceptible to engulfment by phagocytes. Vascular permeability mediators increase the permeability of the capillaries to allow more plasma and complement fluid to flow to the site of infection. They also encourage PMN to adhere to the walls of capillaries (**margination**) from which they can squeeze through in a matter of minutes to arrive at a damaged area. Once phagocytes do their job, they die and the damaged tissue and fluid form pus.

Each of the cells in the innate immune system binds to antigen using **pattern-recognition receptors**. These receptors are encoded in the germ line of each person. This immunity is passed from generation to generation. Over the course of human development these receptors for pathogen-associated molecular patterns have evolved via natural selection to be specific to certain characteristics of broad classes of infectious organisms.

## 5.7 ADAPTIVE OR ACQUIRED IMMUNITY

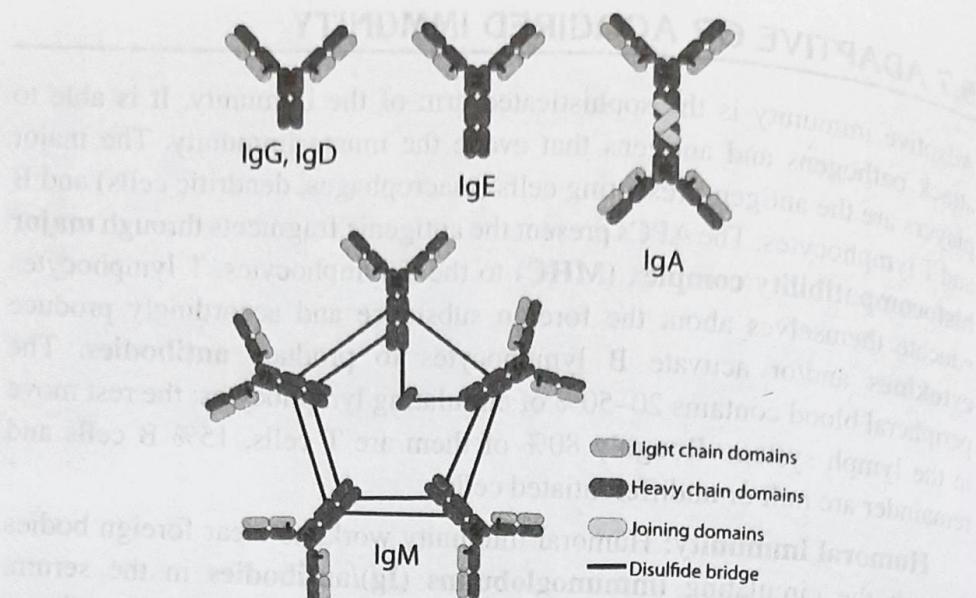
Adaptive immunity is the sophisticated arm of the immunity. It is able to attack pathogens and antigens that evade the innate immunity. The major players are the antigen-presenting cells (macrophages, dendritic cells) and B and T lymphocytes. The APCs present the antigenic fragments through **major histocompatibility complex (MHC)** to the T lymphocytes. T lymphocytes educate themselves about the foreign substance and accordingly produce **cytokines** and/or activate B lymphocytes to produce **antibodies**. The peripheral blood contains 20–50% of circulating lymphocytes; the rest move in the lymph system. Roughly 80% of them are T cells, 15% B cells and remainder are null or undifferentiated cells.

**Humoral immunity:** Humoral immunity works to clear foreign bodies through the circulating **immunoglobulins (Ig)/antibodies** in the serum. Antibodies are proteins secreted by the B lymphocytes. After the antigens attach to the B cell receptor (BCR are nothing but immunoglobulins) on the surface of the B lymphocytes, the cells are made to produce antibodies for the elimination of the antigen. An immature B-lymphocyte is stimulated to maturity when an antigen binds to its surface receptors and there is a T helper cell nearby (to release a cytokine). This **sensitizes or primes** the B cell and it undergoes **clonal selection**, which means it reproduces asexually by mitosis. Most of the family of clones becomes plasma cells. These cells, after an initial lag, produce highly specific antibodies. The other B cells become long-lived **memory cells**.

**Antibodies**, also called **immunoglobulins** or Ig's constitute the *gamma globulin* part of the blood proteins (Fig. 5.11). They are soluble proteins secreted by the B cells. The antibodies inactivate antigens by, (a) **complement fixation** (proteins attach to antigen surface and cause holes to form, i.e., cell lysis), (b) **neutralization** (binding to specific sites to prevent attachment—this is the same as taking their parking space), (c) **agglutination** (clumping), (d) **precipitation** (forcing insolubility and settling out of solution), and other more arcane methods.

Constituents of gamma globulin are: IgG-76%, IgA-15%, IgM-8%, IgD-1%, and IgE-0.002% (responsible for autoimmune responses, such as allergies and diseases like arthritis, multiple sclerosis, and systemic lupus erythematosus). IgG is the only antibody that can cross the placental barrier to the fetus and it is responsible for the 3 to 6 month immune protection of newborns that is conferred by the mother.

IgM is the dominant antibody produced in primary immune responses,

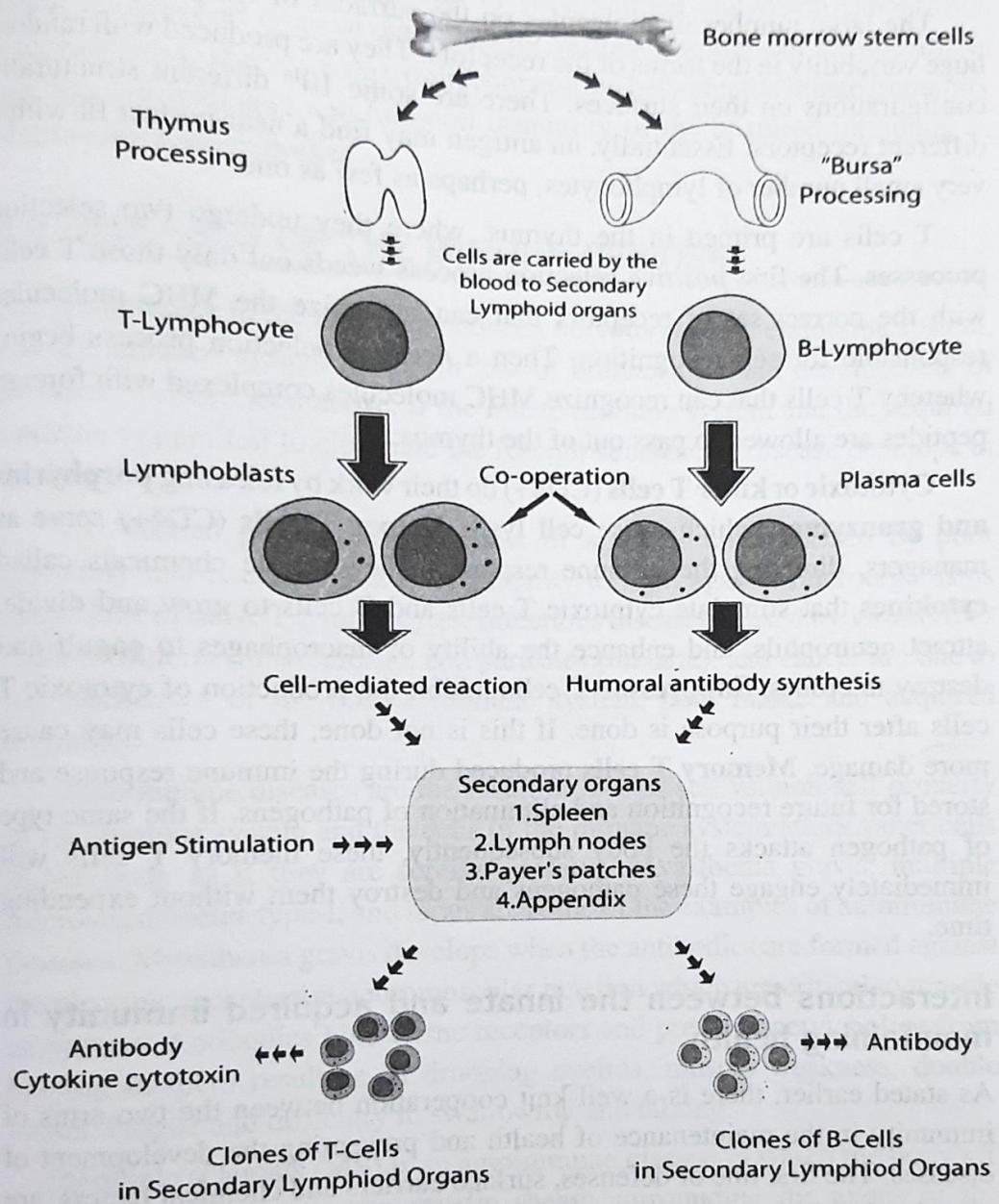


**Fig. 5.11** Five different types of antibodies (immunoglobulins) that belong to humoral immunity.

while IgG dominates in secondary immune responses. IgM is physically much larger than the other immunoglobulins. There are many degrees of flexibility of the antibody molecule. This freedom of movement allows it to more easily conform to the various pockets of binding on an antigen. The upper part or Fab (antigen binding) portion of the antibody molecule (physically and not necessarily chemically) attaches to specific proteins [called epitopes] on the antigen. Thus, antibody recognizes the epitope and not the entire antigen. The Fc region is crystallizable and is responsible for effector functions, i.e., the end to which immune cells can attach. The B cells can produce as many as  $10^{14}$  conformationally different forms of these antibodies.

There are two fundamental adaptive mechanisms: cell-mediated immunity and humoral immunity. **B cells** are produced from the **stem cells** of the bone marrow; they produce antibody and oversee humoral immunity. **T cells** are non-antibody-producing lymphocytes which are also produced in the bone marrow but sensitized in the **thymus** and constitute the basis of cell-mediated immunity. The production of these cells is represented in the figure below.

**Cell-mediated immunity:** Macrophages engulf antigens, process them internally, and then display parts of them on their surface together with some of their own proteins (Fig. 5.12). This sensitizes the T cells to recognize these antigens. All cells are coated with various substances. CD stands for cluster



**Fig. 5.12** Schematic representation of the cooperation between T lymphocytes (cell-mediated immunity) and B lymphocytes (humoral immunity) in eliminating the pathogens

of differentiation and there are more than one hundred and sixty clusters, each of which is a different chemical molecule that coats the surface. CD8+ is read as "CD8 positive." Every T and B cell has about  $10^5$  molecules on its surface. B cells are coated with CD21, CD35, CD40, and CD45 in addition to other non-CD molecules. T cells have CD2, CD3, CD4, CD28, CD45R, and other non-CD molecules on their surfaces.

The large number of molecules on the surfaces of lymphocytes allows huge variability in the forms of the receptors. They are produced with random configurations on their surfaces. There are some  $10^{18}$  different structurally different receptors. Essentially, an antigen may find a near-perfect fit with a very small number of lymphocytes, perhaps as few as one.

T cells are primed in the thymus, where they undergo two selection processes. The first *positive* selection process weeds out only those T cells with the correct set of receptors that can recognize the MHC molecules responsible for self-recognition. Then a *negative* selection process begins whereby T cells that can recognize MHC molecules complexed with foreign peptides are allowed to pass out of the thymus.

**Cytotoxic or killer T cells** (CD8+) do their work by releasing **porphyrins and granzymes**, which cause cell lysis. **Helper T cells** (CD4+) serve as managers, directing the immune response. They secrete chemicals called **cytokines** that stimulate cytotoxic T cells and B cells to grow and divide, attract neutrophils, and enhance the ability of macrophages to engulf and destroy microbes. **Suppressor T cells** inhibit the production of cytotoxic T cells after their purpose is done. If this is not done, these cells may cause more damage. **Memory T cells** produced during the immune response are stored for future recognition and elimination of pathogens. If the same type of pathogen attacks the body subsequently, these memory T cells will immediately engage these pathogens and destroy them without expending time.

### **Interactions between the innate and acquired immunity in maintaining health**

As stated earlier, there is a well-knit cooperation between the two arms of immunity in the maintenance of health and preventing the development of diseases. The first line of defenses, surface barriers and chemical factors, are effective in eliminating majority of the foreign substances. Any substance that pierces the first line of defense primes the cellular component of the innate immunity. PMN leukocytes are the first to arrive followed by macrophages, NK cells and dendritic cells. If the efforts of PMN leukocytes and NK cells fail, the antigen-presenting cells, macrophages and dendritic cells, process the antigen into small fragments and present them through MHC. Once the T lymphocytes get to understand the nature of the antigen, they proliferate (increase their numbers) and start producing cytokines. Cytokines eliminate pathogens through a number of mechanisms such as through proliferation of lymphocytes, priming the B lymphocytes to produce

specific antibodies, and induction of programmed cell death (apoptosis). There are different types of cytokines for various diseases but are specific in their functions. There is a very tight cooperation between the innate immunity and the cell-mediated and humoral immunity of the acquired immunity in eliminating foreign bodies.

## **5.8 DISEASES OF THE IMMUNE SYSTEM**

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Any disturbance in the harmony between nervous system, endocrine system, and the immune system results in loss of homeostasis and development of diseases. As described above, if the innate immune system and the acquired immune system fail to eliminate the foreign substances, disease develops in the body.

The normal physiological process of aging is characterized by poor immunity that is characterized by inability to fight against microorganisms due to lack of naïve T lymphocytes. Infectious diseases caused by virus (HIV/AIDS), bacteria (tuberculosis), and parasites (malaria), and cancer are due to the breakdown of the body's immune system, both innate and acquired immunity.

Autoimmune diseases are the result of loss of self vs. non-self property of the immune system and the cells of the immune system attack other cells of the body as if they are foreign proteins. Myasthenia gravis, multiple sclerosis, diabetes type-I, and lupus are some of the examples of autoimmune diseases. Myasthenia gravis develops when the antibodies are formed against the nicotinic receptors at neuromuscular junction which are critical to muscle movement. Antibodies bind to the receptors and prevent acetylcholine from binding to them resulting in drooping eyelids, muscle weakness, double vision, fatigue and difficulty in swallowing and talking.

Multiple sclerosis (MS) is an autoimmune disease in which the body's T lymphocytes attack its own myelin sheath surrounding the axons of the neurons of the brain and spinal cord. This causes the nerve impulses to move very slowly across the nerve fibers leading to rigidity of limbs, visual problems, pain, numbness, tingling sensation, difficulty in walking, etc. The causative factors are yet to be determined.

## **5.9 IMMUNE ENGINEERING**

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The complexity of the immune system can be compared to that of the brain. There is a vast number of cells, molecules, and organs that compose the

immune system, and these have to act in concert, and together with other vital systems, so as to promote and maintain life. Neither can the immune system act in isolation to maintain life, nor can a higher organism live without an immune system. A unique property of the immune system is that it can act specifically and at the same time has diversity in its functions. The property of “redundancy,” which means “repetition” is helpful in fighting the disease within the body but at the same time makes it difficult to develop effective strategies to fight diseases.

*Artificial immune systems (AIS) compose a new computational intelligence approach inspired by theoretical and experimental immunology with applications to problem solving.* Like all new approach, the field still lacks a more formal description and better theoretical foundations. The term *immune engineering* was coined by Fernando Von Zuben and Leandro Nunes de Castro in 2001. It refers to “...a meta-synthesis process that is going to define the tool for solving a given problem based upon the features of the problem itself, and then apply it to obtain the solution to the problem. Instead of trying to create accurate models of the immune system, the immune engineering develops and implements pragmatic models inspired by the immune system. These must preserve some of the essential properties of the immune system which demonstrate to be implementable and efficient for the development of engineering tools.”

The application of mathematical analysis and modeling to immunology may result in outcomes such as a deeper and more quantitative description of how the immune system works, a more critical analysis of hypothesis, it can assist in the prediction of behaviors and the design of experiments.

With the increasing incidence of different kinds of diseases, Swine Flu, Avian influenza, etc, it becomes necessary to find ways to combat these diseases to ensure health of mankind. Mathematical modeling, computational modeling (immunoinformatics), genetic engineering, molecular biology, etc may be some of the tools to fine-tune the immune system so that it can effectively mount a response in case of elderly and patients with infectious diseases, autoimmune diseases, and cancer.

## **5.10 GENERAL PRINCIPLES OF CELL SIGNALING**

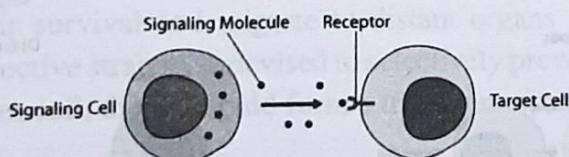
Cell signaling is communication between the cells in order to regulate their activities and maintain basic functions of the cells. This mechanism of cellular communication has been in existence for a long period in the unicellular

organisms such as yeast before the sophisticated signaling mechanisms appeared in multicellular organisms. It took several million years for the multicellular organism to evolve that may have been related to the difficulty of developing the elaborate cell communication mechanisms needed for its survival.

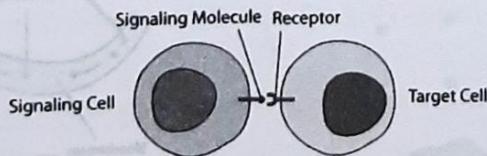
Unicellular organisms such as yeast communicate with each other especially for mating by releasing a few small peptides. However, the cells within higher animals communicate by secreting several types of signal molecules that include proteins, small peptides, amino acids, nucleotides, fatty acid derivatives, steroids, gases such as nitric oxide and carbon monoxide, and immune molecules such as cytokines. The cells release some of these signal molecules into the surrounding extracellular space by a specialized process called exocytosis while others diffuse across the plasma membrane.

Irrespective of the type of signal molecules, the target cell receives the extracellular signal molecule (**ligand**) through a specialized structure called **receptor** (Fig. 5.13). The signal molecule specifically binds to the receptor

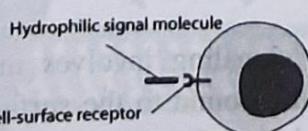
#### 1) Signaling by Secreted molecules



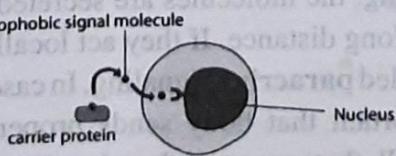
#### 2) Signaling by Plasma-Membrane-Bound Molecule



#### 3) Cell-surface Receptors



#### 4) Intracellular Receptors



**Fig. 5.13** Intercellular signaling in animals.

and sets off a series of reactions within the cell that alters the behavior of the cell. The ligand can act at very low concentrations and the receptors that recognize them bind with high affinity. In most cases, the receptors are transmembrane proteins present on the cell surface but in some cases the receptors are present inside the target cell. This necessitates the transport of signal molecules through diffusion across the plasma membrane which then bind to the receptors in the cytoplasm or nucleus. Such molecules are hydrophobic in nature and are carried in bloodstream bound to a carrier protein.

**Secreted molecules mediate their effects through Contact-dependent, Paracrine, Synaptic, Endocrine and Autocrine signaling (Fig. 5.14)**

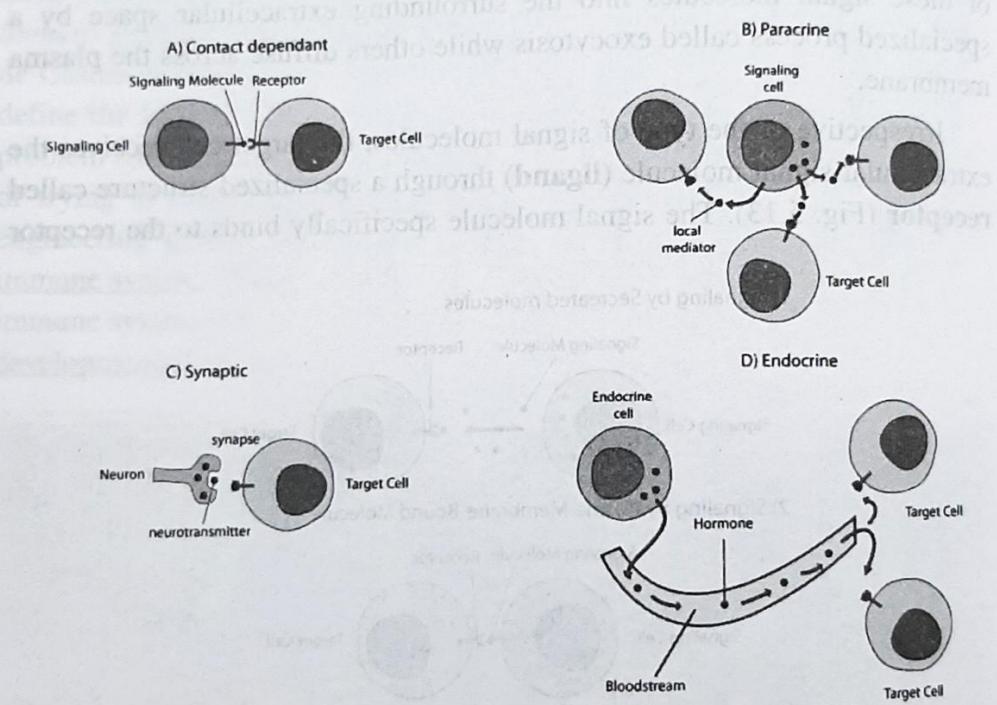


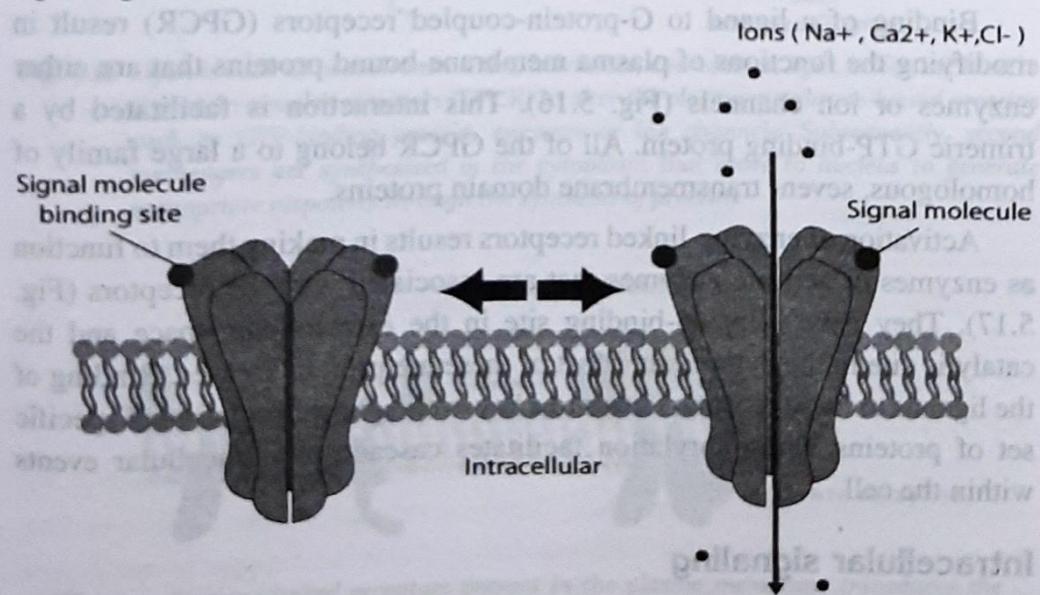
Fig. 5.14 *Different forms of signaling mediated by secreted molecules.*

The **contact-dependent** signaling involves influencing the cell that contacts the signaling molecule bound to the surface of the signaling cell. Such interactions take place during development and immune responses. In other types of signaling, the molecules are secreted and transported either to a short distance or a long distance. If they act locally within a short distance, then the process is called **paracrine** signaling. In case of complex multicellular organism, it is important that body sends proper signals to cells located farthest from the cell that secretes the signaling molecule. As described earlier, the neurons are very effective communicators facilitating this long-

distance communication. The **synaptic** signaling is mediated through **neurotransmitters** that are produced within the cell body and released at the axon terminals to initiate action potential. These electrical impulses are progressively transmitted to long distances to facilitate proper actions at the target cell. Another kind of signaling involves **endocrine** cell. Endocrine cells secrete **hormones** that are carried in the blood to target cells distributed throughout the body.

Neurotransmitters and hormones differ in their functional capabilities. Neurotransmitters are fast while hormones are slow in mediating their effects. Neurotransmitters are released at higher concentrations because they act locally and removed faster while hormones are secreted at lower concentrations and remain in blood for a longer duration.

**Autocrine** signaling involves sending signals to other cells that are of the same type or to themselves. This is mostly seen in development where it can influence cells of similar type to multiply and form tissues. Also, it is observed in immune responses when there is requirement of increased number of cells to fight against the invading foreign protein. Cytokines produced by a single cell facilitate the proliferation of same type of cells to effectively eliminate the microorganism. The same process also favors a cancer cell to multiply and promote their survival and migrate to distant organs in the body and colonize. If an effective strategy is devised to selectively prevent this autocrine signaling in cancer cell, then it would form a treatment option.



**Fig. 5.15** Binding of a ligand to ionotropic receptors facilitate the opening of ion channels resulting in rapid signaling mechanism