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## Neuronal Signaling/ Development and Regeneration (Background Information I)

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**NOTES TO ACCOMPANY LECTURES by John Nicholls,** consisting of chapter summaries taken from the book**:**
**FROM NEURON TO BRAIN** FOURTH EDITION
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# Principles of Signaling and Organization

THIS INTRODUCTION PROVIDES A FRAMEWORK for approaching chapters that deal with signaling, development, and functions of the nervous system in detail. Readers who are curious about the brain but unfamiliar with neurobiology often face certain difficulties in coming to grips with the subject. For example, the terminology of neurobiology, derived from anatomy, electricity, biochemistry, and molecular biology, is disconcerting. But because of the elaborate structure of the nervous system and the specialized features of neural signaling, it is unavoidable.

To describe signals in nerve cells (neurons) and to correlate such signals with our perception of the outside world, we have chosen the retina. The orderly structure of the retina, where the initial steps that lead to vision occur, makes it possible to follow signals literally from neuron to brain.

Information is transmitted in nerve cells by electrical signals. An essential task is to decode the content of the information they transmit. This decoding depends on where nerve fibers arise and where they go. Signals in the optic nerve carry visual information from the retina; similar impulses in a sensory nerve in the fingertip convey information about touch. Within the brain, individual nerve cells receive inputs from thousands of fibers. By integrating this information the cell creates a new message. This message can convey a complex meaning, such as the presence of a vertical bar of light in one's field of vision, or the movement of a tactile stimulus along one's finger.

One simplifying feature in the retina and throughout the nervous system is that nerve cells with similar properties are grouped together in layers or clusters. Another is that the brain uses stereotyped electrical signals to process information. The signals consist of changes in voltage produced by electrical currents flowing across cell membranes. Neurons use only two types of electrical signals: localized graded potentials, which spread over short distances, and action potentials, which are conducted rapidly over long distances.

Neurons transmit information to their targets by releasing chemical transmitter molecules at specialized junctions (known as synapses). The transmitter reacts with specific chemoreceptor molecules in the

membrane of the target cell. This interaction gives rise to a localized graded potential that excites or inhibits the cell depending on the transmitter and the receptors involved. The efficacy of synaptic transmission is modified by use, hormones, and drugs.

During development, neurons depend on molecular signals derived from other cells. These signals determine the shape and position of the neuron, its survival, its transmitter, and the targets to which it connects. Once mature, most nerve cells cannot divide. Molecules in the environment of a neuron influence its capacity for repair after injury.

# .Ion Channels and Signaling

In Chapter 1 we discussed how the transfer of information in the nervous system is mediated by two types of electrical signals in nerve cells: graded potentials that are localized to specific regions of the nerve cell membrane, and action potentials that are propagated along the entire length of a neuronal process. These signals are superimposed on a steady electrical potential across the cell membrane called the resting membrane potential. Depending on cell type, nerve cells at rest have steady membrane potentials ranging from about –30 mV to almost –100 mV, the negative sign meaning that the inside of the membrane is negative with respect to the outside.

Signaling in the nervous system is mediated by changes in the membrane potential: In sensory receptors, an appropriate stimulus, such as touch, sound, or light, causes local **depolarization** (making the membrane potential less negative) or **hyperpolarization** (membrane potential more negative). Similarly, neurotransmitters at synapses act by de-
polarizing or hyperpolarizing the postsynaptic cell. Action potentials, which are large, brief pulses of depolarization, propagate along axons to carry information from one place to the next in the nervous system.

All such changes in membrane potential are produced by the movement of ions across the nerve cell membrane. For example, inward movement of positively charged sodium ions reduces the net negative charge on the inner surface of the membrane or, in other words, causes depolarization. Conversely, outward movement of positively charged potassium ions results in an increase in net negative charge, causing hyperpolarization, as does inward movement of negatively charged chloride ions.

How do ions move across the cell membrane, and how is their movement regulated? The major pathway for rapid movement of ions into and out of the cell is through **ion channels**, which are protein molecules that span the membrane and form pores through which ions can pass. Ion currents are regulated by controlling the opening and closing of such channels. Knowledge of the functional behavior of ion channels has provided an essential advance in our understanding of how electrical signals are generated.


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## Summary

∞ Neurons are connected to each other in a highly specific manner.

∞ At synapses, information is transmitted from cell to cell.

∞ In relatively simple circuits, such as the retina, it is possible to trace connections and understand the meaning of signals.

∞ Neurons within the eye and the brain act as building blocks for perception.

∞ Signals in neurons are highly stereotyped and similar in all animals.

∞ Action potentials conduct unfailingly over long distances.

∞ Local graded potentials depend on passive electrical properties of nerve cells and spread only over short distances.

∞ Owing to the peculiar structure of neurons, specialized cellular mechanisms are required for axonal transport of proteins and organelles to and from the cell body.

∞ During development, neurons migrate to their final destinations and become connected to their targets.

∞ Molecular cues provide guidance for growing axons.

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# STRUCTURE OF ION CHANNELS

THE MOLECULAR STRUCTURE OF ION CHANNELS can be resolved and related to their function by a variety of experimental methods. These include biochemical isolation of channel proteins, molecular cloning to determine amino acid sequences of the proteins, site-directed mutagenesis to alter the sequences in selected locations, and expression of channel proteins in host cells, such as Xenopus oocytes, to examine channel function. In addition, high-resolution electron microscopy, and electron and X-ray diffraction, make it possible to determine the physical conformation of channels.

These combined experimental approaches have been applied most extensively to a ligand-activated channel, the nicotinic acetylcholine receptor. This receptor is composed of five separate subunits arranged around a central core. Two of these—the $\alpha$ subunits—contain receptors for the ligand. Each subunit contains four membrane-spanning regions (designated M1, M2, M3, and M4), connected by intracellular and extracellular loops. The five M2 regions have been identified as lining the pore and forming the gating structure of the channel. The acetylcholine receptor is representative of a genetic superfamily of ligand receptors that includes receptors for glycine, $\gamma$-aminobutyric acid, and serotonin.

Voltage-activated channels form another superfamily. Experimental evidence indicates that the voltage-activated sodium channel is a single large molecule with four repeating domains arranged around a central core, each with six transmembrane segments (designated S1–S6). In each domain the loop of amino acids between S5 and S6 dips into the center of the structure to contribute to the pore lining. Voltage-activated calcium channels have a similar structure. Voltage-activated potassium channels are similar in molecular configuration, but with one important difference: Instead of being single molecules, they are assembled from four separate subunits.

Amino acid sequences and partial structural information have been obtained for a number of other families of receptors and channels. With few exceptions, all are made up of an array of subunits, each subunit containing at least two transmembrane regions, and each with a potential pore-forming loop.


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## SUMMARY

∞ Nicotinic acetylcholine receptors from the electric organ of *Torpedo* consist of five subunits (two α, and three others, designated β, γ, and δ) arranged around a central pore. The α subunits contain the binding sites for ACh.

∞ In each subunit of the AChR the string of amino acids folds to form four membrane-spanning segments (M1–M4) joined by intracellular and extracellular loops. The M2 region has been shown to be associated with the pore lining of the channel.

∞ Eleven distinct nicotinic AChR subunit isoforms have been isolated from nervous tissues, eight having ACh-binding sites (and therefore designated as $\alpha_2$–$\alpha_9$), and three others ($\beta_2$–$\beta_4$). Most α–β combinations can form channels in host cells.

∞ Subunits of receptors for γ-aminobutyric acid (GABA), glycine, and serotonin (5-HT) are analogous in structure to the family of ACh receptor subunits. Together these four receptor families form a superfamily of common genetic origin.

∞ The voltage-activated sodium channel from eel electric organs is a single molecule of about 1800 amino acids, within which are four repeating domains (I–IV). The domains are architecturally equivalent to the subunits of other channels; within each there appear to be six membrane-spanning regions (S1–S6) connected by intracellular and extracellular loops. The eel channel is representative of a diverse family of channel isotypes present in muscle and brain.

∞ The family of voltage-activated calcium channel proteins is analogous in structure to the voltage-activated sodium channel. Voltage-activated potassium channels are structurally similar, but with an important genetic difference: The four repeating units are expressed as individual subunits, not as repeating domains of a single molecule. There are at least 20 distinct potassium channel subunit genes, grouped into four subfamilies. Together, the voltage-activated sodium, calcium, and potassium channels constitute a genetic superfamily.

∞ Subunits of other ligand-activated and voltage-activated channel types vary considerably in size and amino acid composition. Some resemble voltage-activated channel subunits, but most differ markedly from members of both the voltage-activated and the AChR superfamilies. Some have only two or three membrane-spanning regions, others as many as 10.

# IONIC BASIS OF THE RESTING POTENTIAL

AT REST, A NEURON HAS A STEADY ELECTRICAL POTENTIAL across its plasma membrane, the inside being negative with respect to the outside. In relation to the extracellular fluid, the neuron has a high intracellular potassium concentration and low intracellular concentrations of sodium and chloride, so that potassium tends to diffuse out of the cell and sodium and chloride tend to diffuse in. The tendency for potassium and chloride to diffuse down their concentration gradients is opposed by the membrane potential. In a model cell permeable only to potassium and chloride, the concentration gradients and the membrane potential can be balanced exactly so that there is no net flux of either ion across the membrane. The membrane potential is then equal to the equilibrium potential for both potassium and chloride.

In the model cell, changing the extracellular potassium concentration changes the potassium equilibrium potential, and hence the membrane potential. In contrast, changing the extracellular chloride concentration eventually leads to a change in intracellular chloride. As a result the chloride equilibrium potential and the membrane potential are unchanged.

Real cells are also permeable to sodium. At rest, sodium ions constantly move into the cell, reducing the internal negativity of the membrane. As a result, potassium, being no longer in equilibrium, leaks out. If there were no compensation, these fluxes would lead to changes in the internal concentrations of sodium and potassium. However, the concentrations are maintained by the sodium–potassium exchange pump, which transports sodium out and potassium in across the cell membrane in a ratio of 3 sodium to 2 potassium. The resting membrane potential depends on the potassium equilibrium potential, the sodium equilibrium potential, the relative permeabilities of the cell membrane to the two ions, and the pump ratio. At the resting potential, the passive fluxes of sodium and potassium are exactly matched by the rates at which they are transported in the opposite direction. Because the sodium–potassium exchange pump transports more positive ions outward than inward across the membrane, it makes a direct contribution of several millivolts to the membrane potential.

The chloride equilibrium potential may be positive or negative with respect to the resting membrane potential, depending on chloride transport processes. Although the chloride distribution plays little role in determining the resting membrane potential, a substantial chloride permeability is important in some cells for electrical stability.

Electrical signals are generated in nerve cells and muscle fibers primarily by changes in permeability of the cell membrane to ions such as sodium and potassium. Increases in permeability allow ions to move inward or outward across the cell membrane down their electrochemical gradients. As we discussed in Chapter 2, permeability increases are due to activation of ion channels. Ions moving through the open channels change the charge on the cell membrane, and hence change the membrane potential. In order to understand how signals are generated, it is necessary to understand the nature of the standing ionic gradients across the cell membrane, and how these influence the resting membrane potential.

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## SUMMARY

• Nerve cells have a high intracellular concentration of potassium and low intracellular concentrations of sodium and chloride, so that potassium tends to diffuse out of the cell, and sodium and chloride tend to diffuse in. The tendency for potassium and chloride to diffuse down their concentration gradients is opposed by the electrical potential across the cell membrane.

• In a model cell permeable only to potassium and chloride, the concentration gradients can be balanced exactly by the membrane potential, so that there is no net flux of either ion across the membrane. The membrane potential is then equal to the equilibrium potential for both potassium and chloride.

• Changing the extracellular potassium concentration changes the potassium equilibrium potential, and hence the membrane potential. Changing the extracellular chloride concentration, on the other hand, leads ultimately to a change in intracellular chloride, so that the chloride equilibrium potential and the membrane potential differ from their original values only transiently.

• The plasma membranes of real cells are permeable to sodium, as well as to potassium and chloride. As a result, there is a constant passive influx of sodium into the cell, and an efflux of potassium. These fluxes are balanced exactly by active transport of the ions in the opposite directions, in the ratio of 3 sodium to 2 potassium. Under these circumstances, the membrane potential depends on the sodium equilibrium potential, the potassium equilibrium potential, the relative conductance of the membrane to the two ions, and the pump ratio.

• Because the sodium–potassium exchange pump transports more positive ions outward than inward across the membrane, it makes a direct contribution of several millivolts to the membrane potential.

• The chloride equilibrium potential may be positive or negative with respect to the resting membrane potential, depending on chloride transport processes. Although the chloride distribution plays little role in determining the resting membrane potential, a high chloride permeability is important for electrical stability.

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# IONIC BASIS OF THE ACTION POTENTIAL

THE IONIC MECHANISMS RESPONSIBLE FOR GENERATING action potentials have been described quantitatively by using the voltage clamp method to measure membrane currents. From such measurements it is possible to determine which components of the currents are carried by different ion species, and to deduce the magnitude and time course of the underlying changes in ionic conductances. Such experiments have shown that depolarization increases sodium conductance and, more slowly, potassium conductance. The activation of sodium conductance is transient, being followed by inactivation. The increase in potassium conductance persists for as long as the depolarizing pulse is maintained. The dependence of sodium and potassium conductances on membrane potential and their sequential timing account quantitatively for the amplitude and time course of the action potential, as well as for other phenomena, such as threshold and refractory period.

Patch clamp experiments have been used to examine the behavior of individual sodium and potassium channels associated with the action potential. The behavior of the channels is consistent with previous voltage clamp experiments on whole cells: Depolarization increases the probability that sodium and potassium channels will open. For both ion channels the increase in this probability follows the same time course as that of the corresponding voltage clamp currents. For example, sodium channels open most frequently near the beginning of a depolarizing pulse and openings then become less frequent as inactivation develops.

Other cation channels can be involved in action potential generation. In some cells, voltage-activated calcium channels are responsible for the rising phase of the action potential, and repolarization can involve activation of a variety of potassium channel types.


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## SUMMARY


• The action potential in most nerve cell membranes is produced by a transient increase in sodium conductance that drives the membrane potential toward the sodium equilibrium potential, followed by an increase in potassium conductance that returns the membrane potential to its resting level.

• The increases in conductance occur because sodium and potassium channels in the membrane are voltage-dependent: Their opening probability increases with depolarization.

• Voltage clamp experiments on squid axons have provided detailed information about the voltage dependence and time course of the conductance changes. When the cell membrane is depolarized, the sodium conductance is activated rapidly, then inactivated. Potassium conductance is activated with a delay and remains high as long as the depolarization is maintained.

• The time course and voltage dependence of the sodium and potassium conductance changes account precisely for the amplitude and time course of the action potential, as well as other phenomena, such as activation threshold and refractory period.

• The activation of sodium and potassium conductances by depolarization requires, in theory, charge movements within the membrane. Appropriate charge movements, called gating currents, have been measured.

• Patch clamp experiments on voltage-activated sodium and potassium channels are consistent with voltage clamp experiments and reveal new details about the process of excitation. For example, sodium channels open for a relatively short time, and the probability that they open during a depolariz-ing step first increases and then decreases, corresponding to activation and inactivation of sodium conductance in the whole cell. Various kinetic models have been proposed for channel activation and inactivation.

• Calcium plays an important role in excitation. In some cells calcium influx, rather than sodium influx, is responsible for the rising phase of the action potential. In addition, membrane excitability is controlled by extracellular calcium concentration. As extracellular calcium decreases, excitability increases.

# PROPERTIES AND FUNCTIONS OF NEUROGLIAL CELLS

NERVE CELLS IN THE CENTRAL AND THE PERIPHERAL NERVOUS SYSTEM are surrounded by satellite cells. These consist of Schwann cells in the periphery and neuroglial cells in the CNS. In this chapter we discuss the structure and properties of the satellite cells, their interactions with neurons, and open questions regarding their functions.

Neuroglial cells make up about one-half of the volume of the brain and greatly outnumber neurons. The main classes of neuroglial cells are oligodendrocytes, astrocytes, and radial glial cells. Microglial cells constitute a separate population of wandering phagocytotic cells in the nervous system. Neurons and glial cells are densely packed. Their membranes are separated from each other by narrow fluid-filled extracellular spaces that are about 20 nm wide. Glial cell membranes, like those of neurons, contain channels for ions, receptors for transmitters, ion transport pumps, and amino acid transporters. In addition, glial cells are linked to each other by low-resistance gap junctions that permit direct passage of ions and small molecules. Glial cells, which have more negative resting potentials than neurons, do not generate action potentials.

An essential function of oligodendrocytes and Schwann cells is to form myelin around axons and speed up conduction of the nerve impulse. Glial cells and Schwann cells also guide growing axons to their targets. Microglial cells invade regions of damage or inflammation and phagocytose debris.

By virtue of the close apposition of glial and neuronal membranes, dynamic interactions occur between the two types of cells. Thus, neurons release $K^+$ into narrow extracellular spaces during the conduction of impulses, thereby raising its concentration and depolarizing the glial membrane. Glial cells influence the composition of fluid surrounding neurons by taking up $K^+$, as well as transmitters that accumulate after neuronal activity. Glial cells secrete transmitters, nutrients, and trophic molecules into extracellular space. It is hard to estimate quantitatively the part played by these mechanisms in the normal functioning of neurons.


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## SUMMARY

- Glial cells in the brain and Schwann cells in the periphery envelop neurons.
- Oligodendrocytes have short processes and myelinate larger axons.
- Astrocytes surround brain capillaries.
- Schwann cells myelinate peripheral axons and produce trophic molecules.
- Microglial cells remove debris after damage and are involved in inflammatory responses of the nervous system.
- Glial cells have more negative resting potentials than neurons and do not produce action potentials.
- Glial cells are electrically coupled to each other but not to neurons.
- Glial cell membranes contain ion channels for sodium, potassium, and calcium, as well as receptors, pumps, and transporters.
- Glial cells play roles in development, in regeneration, and in homeostatic control of the fluid environment of neurons.

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# PRINCIPLES OF DIRECT SYNAPTIC TRANSMISSION

SYNAPSES ARE POINTS OF CONTACT between nerve cells and their targets where signals are handed on from one cell to the next. At electrical synapses, current flows from the presynaptic nerve terminal into the postsynaptic cell to alter its membrane potential. Electrical transmission is prevalent in the nervous systems of invertebrates and also occurs at synapses in the mammalian CNS. At chemical synapses, the arrival of the action potential in the presynaptic nerve terminal causes neurotransmitter molecules to be released. At direct chemical synapses, the transmitter binds to ionotropic receptors in the membrane of the postsynaptic cell that are themselves ion channels. As a result, the conformation of the receptor changes, the channel opens, ions flow, and the membrane potential changes. At indirect chemical synapses, metabotropic receptors and intracellular second messengers are involved (Chapter 10).

The channels opened at excitatory synapses allow cations to enter, driving the membrane potential toward threshold. At inhibitory synapses, transmitters open channels that are permeable to anions, tending to keep the membrane potential negative to threshold. At both excitatory and inhibitory synapses, the direction of current flow is determined by the balance of concentration and electrical gradients acting on the permeant ions.

Synapses between motor nerves and muscle fibers provided important preparations for understanding the mechanisms of direct chemical synaptic transmission. In the mammalian central nervous system, directly mediated excitatory and inhibitory transmission occurs at synapses where acetylcholine, glutamate, γ-aminobutyric acid, serotonin, and purines are released to activate ionotropic receptors.

More than one type of transmitter may be released at a single chemical synapse, and many transmitters act both rapidly, by binding to and opening ion channels directly, and more slowly through indirect mechanisms.


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## SUMMARY


• Signaling between nerve cells and their targets can occur by chemical or electrical synaptic transmission.

• Electrical synaptic transmission is mediated by the direct flow of current from cell to cell.

• At chemical synapses a neurotransmitter released from the presynaptic terminal activates receptors in the postsynaptic membrane; the time required for transmitter release imposes a minimum synaptic delay of approximately 1 ms.

• Direct chemical synaptic transmission occurs when the postsynaptic receptor activated by a neurotransmitter is itself an ion channel. Such ligand-activated ion channels are called ionotropic transmitter receptors.

• At direct excitatory synapses, such as the vertebrate skeletal neuromuscular junction, the neurotransmitter (in this case ACh) opens cation-selective channels, allowing sodium, potassium, and calcium ions to flow down their electrochemical gradients.

• The relative permeability of a channel for various ions determines the reversal potential; at excitatory synapses the reversal potential is more depolarized than the threshold for action potential initiation.

• Direct chemical synaptic inhibition occurs when a neurotransmitter opens anion-selective channels, which allow chloride ions to flow down their electrochemical gradient. The reversal potential for such currents is the chloride equilibrium potential ($E_{Cl}$); inhibition occurs if $E_{Cl}$ is hyperpolarized to threshold.

• Many transmitter receptors desensitize; that is, their response decreases during repeated or prolonged transmitter application.

# Indirect Mechanisms of Synaptic Transmission

NEUROTRANSMITTERS BIND TO METABOTROPIC RECEPTORS that influence ion channels and pumps indirectly through membrane-associated or cytoplasmic second messengers. At many synapses in the central and autonomic nervous systems, transmission occurs solely by such indirect mechanisms. At other synapses indirect mechanisms modulate direct transmission.

Indirect synaptic transmission is often mediated by G protein–coupled receptors. G proteins, so called because they bind guanine nucleotides, are trimers of three subunits: $\alpha$, $\beta$, and $\gamma$. When a G protein is activated by its receptor, the $\alpha$ and $\beta\gamma$ subunits dissociate. The free subunits bind to and modulate the activity of intracellular targets. Some G protein subunits bind to ion channels, producing relatively brief effects. For example, when ACh binds to its muscarinic receptor on cells in the atrium of the heart, a G protein is activated. The freed $\beta\gamma$ subunit binds to and opens a potassium channel, thereby slowing the heart.

A second mechanism of G protein action is through activation of enzymes that produce intracellular second messengers. An example is the activation of a G protein in cardiac muscle cells by binding of norepinephrine to $\beta$-adrenergic receptors. The activated $\alpha$ and $\beta\gamma$ subunits stimulate the enzyme adenylyl cyclase. The resulting increase in cyclic AMP activates another enzyme, cAMP-dependent protein kinase, which modifies the activity of channels and enzymes through phosphorylation. Such responses may last for seconds, minutes, or hours, often persisting long after the transmitter interaction with the receptors has stopped. These mechanisms provide an enormous signal amplification.

Potassium and calcium channels are prime targets for such indirect transmitter action. Indirect action can cause channels to be opened, closed, or changed in their voltage sensitivity. Thus, indirectly acting transmitters open potassium channels in heart atrial cells, inhibit N-type calcium channels in sympathetic neurons, and increase the probability that calcium channels will open in response to depolarization in cardiac muscle cells. Changes in channel activation in axon terminals modify transmitter release; in postsynaptic cells such changes alter spontaneous activity and the responses to synaptic inputs.

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## Summary


• Neurotransmitters activate metabotropic receptors in target cells. Metabotropic receptors are not themselves ion channels, rather they modify the activity of ion channels, ion pumps, or other receptor proteins by indirect mechanisms.

• Metabotropic receptors produce their effects through
G proteins. Examples of metabotropic receptors include muscarinic acetylcholine receptors; α- and β-adrenergic receptors; some of the receptors for GABA, 5-HT, dopamine, and glutamate; and receptors for neuropeptides, for light, and for odorants.

• G proteins are αβγ heterotrimers. In the resting state, GDP is bound to the α subunit, and the three subunits are associated as a trimer. When activated by a metabotropic receptor, GDP is replaced with GTP, the α and βγ subunits dissociate, and the free subunits activate one or more intracellular targets. The activity of G protein subunits is terminated by hydrolysis of GTP to GDP by the endogenous GTPase activity of the α subunit, and the recombination of α and βγ subunits into a trimer.

• Some G protein βγ subunits bind directly to ion channels and stimulate or inhibit their activity. Other G protein α or βγ subunits activate adenylyl cyclase, phospholipase C, or phospholipase $A_2$, generating intracellular second messengers that can have widespread effects.

• Indirectly acting transmitters influence the activity of potassium and calcium channels. Changes in channel activity in turn influence the resting potential, spontaneous activity, the response to other inputs, or the amount of calcium entering during an action potential, and thereby the amount of transmitter release.

• Changes in intracellular calcium or calcium–calmodulin concentration regulate ion channels, phospholipases C and $A_2$, protein kinase C, calpain, adenylyl cyclase, cyclic nucleotide phosphodiesterase, and nitric oxide synthase. Both the distribution of changes in intracellular calcium, which can be highly localized, and their dynamics (calcium waves and oscillations) are important determinants of calcium action.

• Transmitter actions mediated by indirect mechanisms have time courses that vary from milliseconds to years. Rapid effects are produced by direct changes in ion channel activity, effects of intermediate duration by activation and phosphorylation of enzymes and other proteins, and very long-lasting effects by regulation of protein synthesis.

# Transmitter Release

THE STIMULUS FOR NEUROTRANSMITTER RELEASE is depolarization of the nerve terminal. Release occurs as a result of calcium entry into the terminal through voltage-activated calcium channels. Invariably a delay of about 0.5 ms intervenes between presynaptic depolarization and transmitter release. Part of the delay is due to the time taken for calcium channels to open; the remainder is due to the time required for calcium to cause transmitter release.

Transmitter is secreted in multimolecular packets (quanta), each containing several thousand transmitter molecules. In response to an action potential, anywhere from 1 to as many as 300 quanta are released almost synchronously from the nerve terminal, depending on the type of synapse. At rest, nerve terminals release quanta spontaneously at a slow rate, giving rise to spontaneous miniature synaptic potentials. There is also at rest a continuous, nonquantal leak of transmitter from nerve terminals.

One quantum of transmitter corresponds to the contents of one synaptic vesicle and comprises several thousand molecules of a low-molecular-weight transmitter. Release occurs by the process of exocytosis, during which the synaptic vesicle membrane fuses with the presynaptic membrane and the contents of the vesicle are released into the synaptic cleft. The components of the vesicle membrane are then retrieved by endocytosis, sorted in endosomes, and recycled into new synaptic vesicles.


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## Summary

• When an axon terminal is depolarized, voltage-activated calcium channels open, increase the intracellular calcium concentration, and cause transmitter release.

• Transmitter is released in multimolecular packets, or quanta, that arise when transmitter-containing synaptic vesicles fuse with the plasma membrane and release their contents by exocytosis. There is also a continuous, nonquantal leak of transmitter from axon terminals at rest.

• The synaptic delay between the beginning of the presynaptic depolarization and the beginning of the postsynaptic potential is due to the time required for the nerve terminal to depolarize, calcium channels to open, and increased intracellular calcium to cause exocytosis.

• Exocytosis occurs at a slow rate at rest, producing spontaneous miniature synaptic potentials. In response to an action potential, anywhere from 1 to 300 quanta are released nearly simultaneously, depending on the synapse.

• Synaptic vesicles contain several thousand molecules of transmitter. The number of postsynaptic receptors activated by a quantum of transmitter varies considerably from about 15 to 1500, depending on the synapse.

• The distribution of amplitudes of spontaneous miniature and evoked postsynaptic potentials can be analyzed by statistical methods to determine the quantum size and quantum content of the response. Neuromodulatory influences that act presynaptically tend to influence quantum content; those that act postsynaptically tend to influence quantum size.

• After exocytosis, synaptic vesicles may flatten out into the plasma membrane. Components of the vesicle membrane are then specifically retrieved by endocytosis of coated vesicles and recycled into new synaptic vesicles. Under certain circumstances, vesicles may pinch back off without ever becoming incorporated into the surface membrane.

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# SYNAPTIC PLASTICITY

THE EFFICACY OF TRANSMISSION AT A SYNAPSE is not fixed, but can vary as a consequence of patterns of ongoing activity. Short trains of presynaptic action potentials can produce either facilitation of transmitter release from the presynaptic terminal that persists for several hundred milliseconds, or depression of release lasting for seconds, or a combination of both. A second phase of facilitation, called augmentation, can also last for seconds. Longer-lasting trains of presynaptic action potentials produce posttetanic potentiation (PTP), an increase in transmitter release that lasts for tens of minutes. A persistent increase in calcium concentration in the presynaptic terminal underlies these changes in release.

At many synapses repetitive activity can produce not only short-term changes, but also alterations in synaptic efficacy that last for hours, or even days. The two phenomena of this type are known as long-term potentiation (LTP) and long-term depression (LTD). LTP is mediated by an increase in calcium concentration in the postsynaptic cell that sets in motion a series of second messenger systems that recruit additional receptors into the postsynaptic membrane and also increase receptor sensitivity. LTD appears to occur in response to smaller increases in postsynaptic calcium concentration and is accompanied by a reduction in the number and sensitivity of postsynaptic receptors.

Other forms of LTP and LTD appear to involve presynaptic mechanisms. Both LTP and LTD have been postulated to be substrates for various forms of learning and memory formation, but current evidence for this idea is inconclusive.


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## Summary


• Short periods of synaptic activation can result in facilitation, depression, or augmentation of transmitter release, or a combination of these effects.

• Facilitation decays gradually over a few hundred milliseconds; synaptic depression and augmentation persist for several seconds.

• Facilitation is related to a persistent increase in cytoplasmic calcium concentration in the presynaptic terminal.

• Longer periods of repetitive stimulation result in posttetanic potentiation (PTP) of transmitter release, which can last for tens of minutes and, like facilitation, is mediated by an increase in presynaptic terminal calcium concentration.

• In various parts of the central nervous system, repetitive stimulation can result in long-term potentiation (LTP) or long-term depression (LTD) of synaptic strength.

• The change in synaptic efficacy during LTP or LTD may be homosynaptic, involving only the stimulated input, or heterosynaptic, affecting adjacent synapses on the same dendrite; in addition, heterosynaptic effects may be associative, requiring the coordinate activation of both synapses.

• LTP is produced by an increase in calcium concentration in the postsynaptic cell, and appears to involve both the insertion of new receptors into the postsynaptic membrane and an increase in receptor sensitivity.

• LTD also requires an increase in postsynaptic calcium concentration and appears to be mediated by a decrease in receptor number and sensitivity.

• Both LTP and LTD can also involve changes in transmitter release from the presynaptic terminal.

• Although there are some correlations between LTP and LTD and behavioral tasks involving learning, no unequivocal relation between these long-term synaptic changes and memory formation have been established.

# Cellular Mechanisms of Integration and behavior in Leeches, Ants and Bees

EXPERIMENTS MADE IN INVERTEBRATES have provided crucial insights into cellular and molecular mechanisms of signaling. Because of their simplified nervous systems and wide diversity, animals such as flies, bees, ants, worms, snails, lobsters, and crayfish offer advantages for studying how nerve cells integrate information to produce coordinated behavior.

One convenient example is the CNS of the leech. In this animal it is possible to identify a single neuron, measure its biophysical properties, trace its connections, and define its role in integrative actions such as reflexes, swimming, and avoidance behavior. The leech CNS consists of 21 stereotyped ganglia, each of which contains only about 400 neurons. Individual sensory cells, motoneurons, and interneurons can be recognized by visual inspection and by recording electrically. Each mechanosensory cell in the ganglion responds selectively to touch, pressure, or noxious stimulation and innervates a well-defined area of skin. Sensory cells transmit information to interneurons and motoneurons by electrical and chemical synapses. After repetitive stimulation at natural frequencies, transmission in sensory neurons becomes blocked at branch points where small axons feed into larger processes. This disconnects sensory neurons from some but not all of their targets temporarily. With circuits consisting of identified neurons, it is also possible to study how individual neurons form connections during development and during regeneration after injury.

Ants and bees exhibit complex behaviors that exemplify an important principle: Measurements of behavior provide insights into integrative mechanisms. Hence, one can work downward from behavior to brain to neuron. From analysis of the path taken by an ant or a bee, one can progress to the properties of the photoreceptors and the wiring that made it possible. Desert ants migrate over long distances while foraging for food. As an ant searches, it moves in a zigzag meandering path. Once the ant has found its

food source, however, it turns toward its nest and marches directly there in a straight line. The CNS keeps track of turns to the left and right that the ant made along its initial trajectory, calculates the position from which it started, and directs it straight for home. Such integration of information depends on coordinates provided by polarized light from the sun. The desert ant's eyes contain specific groups of photoreceptors for polarized light. These photoreceptors supply information to the CNS, which calculates and keeps track of movements in space to create a new vector. Ants and bees exemplify the ability of invertebrate nervous systems containing relatively few neurons to make complex computations. Thanks to their diverse forms, invertebrates constitute appealing preparations for studying cellular mechanisms that underlie behavior.


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## SUMMARY

∞ Invertebrates display a wide range of sophisticated behaviors.

∞ The properties of invertebrate neurons and glial cells resemble those of vertebrates.

∞ Invertebrate nervous systems consist of hundreds or thousands of neurons.

∞ Each type of invertebrate can offer advantages for investigation of a specific type of problem.

∞ Properties of individual nerve cells and synapses can be used to explain the behavior of the animal and its modifications.

∞ Quantitative measurements of behavior shed light on fundamental principles in neurobiology.

∞ Not all work on invertebrate central nervous systems is necessarily directed toward understanding mechanisms in human brain. It is fascinating in its own right.

# AUTONOMIC NERVOUS SYSTEM

THE AUTONOMIC NERVOUS SYSTEM controls essential functions of the vertebrate body. Thus, neurons of the autonomic nervous system supply smooth muscles in the eye, lung, gut, blood vessels, bladder, genitalia, and uterus. They regulate glandular secretion, blood pressure, heart rate, cardiac output, and body temperature, as well as food and water intake. In contrast to speedy conduction and muscle contractions required for limb movements, these "housekeeping" or "vegetative" functions are slower, last longer, and are often less focused.

Four distinct groupings of neurons make up the autonomic nervous system. The sympathetic division consists of neurons, the axons of which leave the spinal cord through ventral roots from thoracic and lumbar segments. They form synapses on nerve cells in sympathetic ganglia situated alongside and at a distance from the spinal cord, and on chromaffin cells in the adrenal medulla. Sympathetic postganglionic axons are unmyelinated and extend over long distances to target areas. The parasympathetic division consists of axons leaving through certain cranial and sacral nerves. They form synapses in ganglia situated within the target organs. Parasympathetic postganglionic axons are in general shorter than those of the sympathetic nervous system. A third, highly complex division consists of millions of nerve cells in the intestinal wall, the enteric nervous system. The fourth division comprises neurons in the spinal cord, hypothalamus, and brainstem. Within the CNS, boundaries between the autonomic and somatic nervous systems are not sharply defined.

Synaptic transmission in the autonomic nervous system is extraordinary in its diversity, including all the known transmitters. Principles of transmission and integration that were revealed at autonomic synapses include the chemical nature of synaptic transmission, reuptake of transmitter, autoreceptors on presynaptic terminals, co-release of more than one transmitter at a single terminal, and the role of second messengers. Transmitters used at autonomic ganglia include acetylcholine acting on both nicotinic and muscarinic receptors, peptides, and dopamine. Postganglionic parasympathetic nerve terminals release acetylcholine as the primary transmitter that acts on muscarinic receptors in the target organs. Postganglionic sympathetic neurons release norepinephrine, epinephrine, acetylcholine, purines, or peptides as primary transmitters. Sympathetic and parasympathetic neurons co-release ATP and peptides. Whereas much is known about the regulation of activity in smooth muscle and gland cells, less information is available about integrative mechanisms within the CNS that regulate autonomic functions.

The periodic 24-hour cycle of activity, known as circadian rhythm, influences many autonomic functions. Experiments in which recordings were made from specific neurons in the hypothalamus have revealed one of the cellular mechanisms that generate the rhythm. Slow increases in intracellular chloride concentration in daytime cause inhibition by $\gamma$-aminobutyric acid (GABA) to be converted to excitation. Thereby firing is increased during the day and decreased at night.

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## Summary

∞ The autonomic nervous system regulates essential functions of all internal organs and is itself regulated by hormonal and sensory feedback.

∞ Parasympathetic effects are focused, compared to the widespread effects of sympathetic activation.

∞ ACh is the principal transmitter used for transmission in autonomic ganglia, at parasympathetic nerve endings, and at certain sympathetic nerve endings.

∞ Norepinephrine is the principal transmitter for most sympathetic endings. Other transmitters include acetylcholine, peptides, and ATP.

∞ A single molecule—for example, LHRH, which is also known as GnRH—can act as a transmitter at synapses and a hormone within the brain.

∞ Analysis of effects mediated by the autonomic nervous system is complex, owing to the variety of receptors and the large numbers of peptide and nonpeptide transmitters.

∞ Epinephrine released as a hormone into the circulation from the adrenal medulla reaches receptors in target cells that are not affected by transmitter released from nerve endings.

∞ The hypothalamus is the region of the brain that controls the overall activities of the autonomic nervous system and also regulates the secretion of hormones.

∞ The hypothalamus itself is influenced by higher centers of the central nervous system and by hormones.

# TRANSDUCTION AND SIGNALING IN THE RETINA

THE WAY IN WHICH NEURONAL SIGNALS ARE EVOKED by light to produce our perception of scenes with objects and background, movement, shade, and color begins in the retina. Responses to light start at receptors known as rods and cones that contain visual pigments. Rods are highly sensitive and can be activated by a single quantum of light. Color and daylight vision depend on cones. Absorption of light by the visual pigment of a photoreceptor activates a G protein, leading to a cascade of biochemical reactions. As a result, nucleotide-gated cation channels in the membrane close, causing the photoreceptor to become hyperpolarized. Light thereby reduces ongoing transmitter release onto postsynaptic bipolar and horizontal cells. Signals from photoreceptors finally reach ganglion cells, whose axons enter the optic nerve and constitute the sole output from the eye.

The connections between receptors and ganglion cells involve bipolar, horizontal, and amacrine cells. Like rods and cones, bipolar and horizontal cells produce graded local potentials, not action potentials. Signaling by individual neurons in the retina and at successive levels of the visual system is best analyzed in terms of receptive fields, which are the building blocks for perception. Receptive field of a neuron in the visual system refers to the restricted area of the retinal surface that, upon illumination, enhances or inhibits the signaling of that cell. The receptive field of a retinal ganglion cell is a small circular area on the retina. Action potentials are evoked in “on” ganglion cells by small spots of light shone onto the center of the field surrounded by darkness, or in “off” cells by small dark spots surrounded by light. Two groups of ganglion cells are functionally important. Known as parvocellular (P) and magnocellular (M), they are distinguished by their sizes, positions, connections, and physiological responses. Smaller P ganglion cells exhibit fine spatial discrimination and color sensitivity. Larger M ganglion cells respond better to moving stimuli and to small changes in contrast. These distinctive properties of M and P divisions are maintained through successive relays in the brain up to consciousness.

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## Summary

∞ Rod and cone photoreceptors respond to illumination in dim and bright light.

∞ The visual pigments are densely packed on rod and cone membranes.

∞ Transduction occurs in a series of steps involving a G protein and cyclic GMP.

∞ In darkness, photoreceptors are depolarized and continuously release glutamate.

∞ Light causes the closing of nucleotide-gated cation channels, hyperpolarization, and reduction of glutamate release.

∞ Two main classes of bipolar cells respond to glutamate released by photoreceptors.

∞ H bipolar cells are depolarized in the dark and hyperpolarized by light.

∞ D bipolar cells are hyperpolarized in the dark and depolarized by light.

∞ Receptive field refers to the area of the visual field or retina, illumination of which influences the signals of a cell in the visual system.

∞ Photoreceptors, horizontal cells, and bipolar cells do not produce action potentials.

∞ Ganglion cells and amacrine cells give action potentials.

∞ Bipolar cells and ganglion cells have concentric receptive fields with “on” or “off” centers and antagonistic surrounds.

∞ Ganglion cells respond poorly to diffuse light.

∞ Large ganglion cells, known as magnocellular, or M, cells have large receptive fields and respond well to movement.

∞ Smaller ganglion cells, known as parvocellular, or P, cells, have smaller receptive fields and respond to color and fine detail.

# SIGNALING IN THE LATERAL GENICULATE NUCLEUS AND THE PRIMARY VISUAL CORTEX

RETINAL GANGLION CELLS PROJECT TO THE LATERAL GENICULATE NUCLEUS, where they form a retinotopic map. The six layers of the mammalian lateral geniculate nucleus are each innervated by one eye or the other, and they receive input from distinct subtypes of retinal ganglion cells, resulting in magnocellular, parvocellular, or koniocellular geniculate layers. Lateral geniculate neurons have center–surround receptive fields like those of retinal ganglion cells.

Lateral geniculate neurons project to and form a retinotopic map in primary visual cortex, $V_1$, also called area 17 or striate cortex. The receptive fields of cortical cells, rather than having a center–surround organization, consist of lines or edges, representing an additional step in visual analysis. The six layers of $V_1$ have specific organizational properties: afferent fibers from the geniculate end primarily in layer 4 (and some in layer 6); cells in layers 2, 3, and 5 receive cortical input. Cells in layers 5 and 6 project to subcortical areas, and cells in 2 and 3 project to other cortical areas. Each vertical stack of cortical cells functions as a module, operating on input from one location in visual space and forwarding the processed information to secondary visual areas. This columnar organization of visual cortex is evident in the constancy of receptive field location throughout the depth of the cortex, and in the segregation of the projection of the two eyes into ocular dominance columns.

Two classes of neurons in $V_1$ have been defined by their response properties. Receptive fields of simple cells are elongated, with adjacent “on” and “off” areas. Thus, the optimal stimulus for a simple cell is a specifically oriented light or dark bar. A complex cell also responds to oriented bars, but the bar can fall in any region of the receptive field. End inhibition of simple or complex cells gives rise to still more detailed stimulus requirements, such as a line of specific length, or a corner in the receptive field.

The receptive fields of simple cells result from the convergent input of a number of geniculate afferents whose adjoining field centers define the receptive area. The fields of complex cells depend on input from simple cells and other cortical cells. The progression of receptive field properties from retina to lateral geniculate, to cortical simple and then complex cells suggests a hierarchical flow of information whereby the neural constructs from one level are combined to produce still more abstract concepts at the next. Throughout the pathways, the emphasis is on contrast and the detection of edges, rather than on diffuse illumination. Thus, the complex cells of the visual cortex can “see” the lines that define the edges of a box, but they care little about the absolute level of light inside that box.

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## Summary

∞ The lateral geniculate nucleus of the thalamus receives input from retinal ganglion cells. Inputs from the two eyes segregate to different layers that are in retinotopic register.

∞ The lateral geniculate layers are functionally distinct, comprising magnocellular, parvocellular, or koniocellular response types.

∞ The six layers of primary visual cortex serve as input and output stages of cortical processing.

∞ Geniculate afferents from the two eyes are segregated in layer 4C of striate cortex, establishing ocular dominance columns that can be detected physiologically and anatomically.

∞ Magnocellular and parvocellular layers of the LGN project specifically to different sublayers of cortical layer 4C.

∞ The receptive field of an LGN cell has a concentric center–surround organization resembling that of a retinal ganglion cell and responds poorly to uniform illumination.

∞ Simple cells of striate cortex respond to oriented light or dark bars. Their receptive fields can be mapped with spots of light as though composed of adjoining lateral geniculate center–surround receptive fields.

∞ Complex cells of striate cortex also respond to oriented bars or edges. However, their receptive fields cannot be mapped with spots of light, but instead result from the convergence of multiple simple cells with adjoining receptive areas.

∞ End inhibition results when an additional suppressive zone specifies the optimal length for a simple or complex cell.

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# FUNCTIONAL ARCHITECTURE OF THE VISUAL CORTEX

THE VISUAL CORTEX IS ORGANIZED INTO VERTICAL CLUSTERS OF CELLS with similar functional attributes. Neurons that are preferentially driven by the right or the left eye are grouped in ocular dominance columns. Orientation columns consist of neurons whose line or edge preferences are at similar angles. The ocular dominance and orientation columns were first discovered by recording electrical activity from series of cortical cells as electrodes traversed the cortical thickness. Ocular dominance and orientation columns

also can be visualized by biochemical and optical techniques that reveal activated regions in the cortex of a living animal.

The axons of magnocellular (M) and parvocellular (P) neurons of the lateral geniculate nucleus project to different subdivisions of layer 4 of primary visual cortex. From here M and P channels distribute differentially to "blobs" and "stripes" revealed by cytochrome oxidase labeling in primary and secondary visual cortex, respectively. Neurons in the M pathway are concerned with the detection of moving stimuli and are sensitive to differences in contrast and depth. Neurons in the P pathway deal with fine detail and color.

During visual perception, features such as color and motion are analyzed separately. This is illustrated by the fact that lesions in discrete regions of the brain result in selective loss of such features, rather than an overall reduction in quality of visual images. Lesions of the parietal cortex in an area known as MT (or $V_5$) lead to loss of motion detection and impairment of depth perception. In the occipitotemporal lobe, lesions of area $V_4$ result in loss of ability to recognize color.

One remarkable development is the use of noninvasive functional magnetic resonance imaging to detect cellular activity in the brains of animals, including humans. Although individual cortical ocular dominance and orientation columns are below the current limit of resolution of this technique, regions of the visual cortex specialized for specific tasks, such as detection of motion or recognition of faces, have been localized.

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## Summary

∞ Neurons in primary visual cortex are organized according to eye preference and orientation selectivity.

∞ The layout of ocular dominance slabs and orientation pinwheels can be visualized by imaging activity-dependent optical signals from the brain surface. Iso-orientation contours tend to intersect ocular dominance domains at right angles, and each orientation domain is shared between two ocular dominance columns.

∞ Magnocellular, parvocellular, and koniocellular pathways form parallel channels from retina to visual cortex. Magnocellular neurons are sensitive to motion and low levels of contrast. Parvocellular neurons signal spatial detail and color. Koniocellular neurons carry color information directly to cytochrome oxidase blobs.

∞ Cytochrome oxidase blobs occur in the center of each ocular dominance column and represent a site of signal synthesis in $V_1$.

∞ Cytochrome oxidase–positive stripes and intervening cortex in $V_2$ are specifically interconnected with blobs in $V_1$.

∞ Visual motion is encoded by neurons in $V_5$ (area MT) in parietal cortex.

∞ Area $V_4$ in occipitotemporal cortex contains a preponderance of color-coded neurons.

∞ Double-opponent color neurons in visual cortex have properties that could contribute to the perceptual phenomenon of color constancy.

∞ Integration of receptive fields in cortex is provided by long horizontal axons that interconnect columns of cells with similar response properties.

∞ Most cortical neurons receive input from corresponding points in the visual field of the two eyes, but some neurons respond to stimuli that fall at different points in the two retinas. Such binocular disparities mediate stereoscopic depth perception in area MT.

∞ Functional magnetic resonance imaging (fMRI) enables primary and secondary visual areas, as well as still more highly specialized regions, to be mapped in human cortex.

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# DEVELOPMENT OF THE NERVOUS SYSTEM

NERVE CELLS ACQUIRE THEIR IDENTITIES AND ESTABLISH ORDERLY and precise synaptic connections during development in response to genetic and environmental influences. These include cell lineage, inductive and trophic interactions between cells, cues that guide cell migration and axon outgrowth, specific cell–cell recognition, and activity-dependent refinement of connections.

The development of the vertebrate nervous system begins with the formation of the neural plate in the dorsal ectoderm. The neural plate then curls to give rise to the neural tube and the neural crest. Neurons and glial cells of the central nervous system are produced by division of precursor cells in the ventricular zone of the neural tube. Postmitotic neurons migrate away from the ventricular surface to form the gray matter of the adult nervous system. Within each region of the developing nervous system the fates of cells become progressively restricted according to anteroposterior, dorsoventral, and local patterns. In the last few years explanations at the molecular level have become available for many aspects of development, such as anteroposterior and dorsoventral patterning, that previously could be described only phenomenologically, with no idea of the underlying mechanisms. For example, the expression of a series of

homeobox genes along the anteroposterior axis establishes the identity of segments in the hindbrain; subsequently the dorsoventral pattern of differentiation is determined, in part, by a gradient of a protein known as Sonic hedgehog.

Neural crest cells form the peripheral nervous system. The phenotype adopted by a neural crest cell is determined by signals from cells in its environment. Thus, a neural crest cell transplanted early in development assumes the fate appropriate to its new location.

To establish synaptic contacts with their targets, neurons extend axons tipped with growth cones that explore the environment. Two classes of molecules have been identified as important substrates for growth cone movements: cell adhesion molecules of the immunoglobulin superfamily and extracellular matrix adhesion molecules. Growth cone navigation is controlled by long- and short-range attractive and repulsive cues. Chemoattractants guide axons either to their ultimate synaptic partners or to an intermediate target, such as a guidepost cell. Chemorepellents prevent axons from entering inappropriate territories. Axonal projections made during development are often more extensive than those seen in the adult, and are trimmed to the adult pattern by trophic and activity-dependent mechanisms.

Functional synaptic contacts are formed rapidly, but at first they lack specializations characteristic of adult junctions. Over the course of several weeks synapses mature to their adult form.

A common feature of vertebrate central nervous system development is an initial overproduction of neurons followed by a period of cell death. Neuronal death is regulated by competition for trophic substances. Nerve growth factor is one member of a family of proteins, called neurotrophins, each of which sustains particular neuronal populations.

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## Summary

∞ During vertebrate embryogenesis, proteins diffuse from the Spemann organizer to induce formation of the neural plate, the edges of which fold upward to form the neural tube.

∞ Cells divide rapidly in the wall of the neural tube. Postmitotic neurons and glial progenitor cells migrate away from the ventricular surface of the neural tube to form the CNS.

∞ Neuronal migration occurs along radial glial cells and pathways marked by cell surface and extracellular matrix components.

∞ The ultimate identity of a cell is determined by cell lineage and inductive interactions.

∞ Homeotic genes are master genes that control and coordinate the expression of groups of other genes, thereby determining the formation of body parts.

∞ In the vertebrate CNS, the fates of developing neurons are first restricted according to anteroposterior position and then by dorsoventral position. The *Hox* family of homeotic genes determines anteroposterior identity in the hindbrain. A protein called Sonic hedgehog, produced by the notochord, induces a ventral fate in cells along the length of the neural tube.

∞ Signals that influence cell differentiation often act through receptor tyrosine kinases, activating complex intracellular signaling cascades that induce changes in gene expression. An example is the regulation of photoreceptor differentiation in *Drosophila*.

∞ In mammalian cerebral cortex, development proceeds in an inside-out fashion. Neurons of the deepest cortical layers are born first.

∞ Neural crest cells arise from the edge of the neural fold and migrate away from the neural tube to form the peripheral nervous system, pigment cells, and bones of the head.

∞ Division of neural stem cells in the central nervous system of adult birds and mammals continually produces new neurons.

∞ The tip of a growing axon expands to form a growth cone.

∞ Cell surface and extracellular matrix adhesion molecules guide growth cones by short-range attractive and repulsive mechanisms.

∞ Netrins act as long-range chemoattractants for many types of axons, semaphorins as long-range chemorepellents.

∞ The ephrins and the Eph family of receptor tyrosine kinases influence pathfinding, cell migration, and cell intermingling by a chemorepellent mechanism.

∞ When a motoneuron growth cone contacts a muscle cell, functional synaptic transmission is established within minutes.

∞ The release of agrin from presynaptic terminals induces the formation of postsynaptic specializations in skeletal muscle.

∞ Neurons rely on trophic factors for survival and differentiation.

∞ Programmed neuronal death is a common feature of neural development.

∞ Synaptic connections, once established, are pruned to ensure appropriate and complete innervation of the target. Pruning occurs through activity-dependent competition among axon terminals for target-derived trophic substances.

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# CRITICAL PERIODS IN VISUAL AND AUDITORY SYSTEMS

THE EFFECTS OF USE AND DISUSE ON THE ESTABLISHMENT of connections have been analyzed in the visual systems of newly born kittens and monkeys. At birth, the receptive fields of neurons in the retina, lateral geniculate nucleus, and visual cortex resemble those of adults, except in layer 4 of the visual cortex. At birth, cortical cells in layer 4 are driven by both eyes. During the first 6 weeks the adult pattern is established so that cells in layer 4 respond to only one eye, while cells in other layers continue to be driven binocularly. Closure of the lids of one eye during the first 3 months of life leads to blindness in that eye and loss of its ability to drive cortical cells. Cortical columns supplied by the deprived eye shrink while those supplied by the normal, undeprived eye expand.

Lid closure in adult animals has no effect on columnar architecture or responses. During the critical period, changes produced by sensory deprivation are reversed by opening the sutured eye and closing the undeprived eye. Additional evidence for competition between the two eyes is provided by experiments made with both eyes closed in early life. When neither eye has an advantage, normal columnar structure develops; however, each cell in the cortex is driven by only one eye. Similarly, when strabismus is produced by cutting extraocular muscles in immature monkeys, few cortical neurons are driven by both eyes, although each eye receives its normal input. The role of activity in competition is shown by experiments in which blockade of impulses in both optic nerves with tetrodotoxin prevents segregation of ocular dominance columns. Spontaneous impulse activity and neurotrophins can contribute to the formation of appropriate connections.

In immature owls, development of the auditory system exhibits critical periods. Prisms placed over the eyes result in displaced receptive field positions. A mismatch thereby occurs between maps of space in the tectum corresponding to visual and auditory inputs. During the first months of life this discrepancy becomes corrected by remapping of auditory fields in the tectum. After a critical period such shifts no longer occur. In owls brought up in an enriched environment with enhanced sensory experience, the critical period during which maps can be brought into register is prolonged. Sensory deprivation experiments are significant for considering the development of higher brain functions.


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## SUMMARY

∞ Receptive fields and cortical architecture in newly born monkeys and kittens resemble those of adults in many respects.

∞ In layer 4 of the cortex, however, geniculate axons overlap and cells are driven by both eyes instead of one during the first 6 weeks of life.

∞ A critical period of about 3 months exists after birth during which closure of the lids of one eye causes changes in structure and function.

∞ Closure of the lids of one eye leads to blindness in that eye.

∞ Cortical cells are no longer driven by the deprived eye, and its ocular dominance columns shrink.

∞ After the critical period, closure of lids or enucleation of an eye does not change cortical architecture.

∞ Binocular lid closure and induction of squint during the critical period do not cause changes in ocular dominance columns but do prevent binocular responses.

∞ Such results suggest that the two eyes compete for cells in the visual cortex.

∞ In newly born owls, the processing of auditory inputs is modified by sensory input during a critical period.

∞ Enrichment of experience in early life increases the duration of the critical period.