Overview

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Anatomy and Physiology of the Brain

The brain is a remarkably complex organ both in its structure and function. At the macroscopic level, it can be divided into three major components: (1) brainstem (which includes medulla, pons, and midbrain), (2) cerebellum (with its cortex and deep nuclei), and (3) cerebral hemispheres (which are composed of cerebral cortex, subcortical white matter, basal ganglia and thalamus, limbic system, and hypothalamus and pituitary). The cerebral cortex itself is divided into frontal, parietal, temporal, and occipital lobes (Fig. 1). At the microscopic level, there are two primary cell types: (1) neurons (which receive, process, and transmit information by electrical and biochemical changes mediated, in part, by neurotransmitters) and (2) glia (which are a diverse group of cells with expanding roles in brain function).

The various macroscopic regions of the brain are responsible for different physiological functions. The brainstem contains nuclei required for autonomic functions, such as regulation of heart rate and respiration. Most cranial nerves, which provide motor and sensory function to structures of the cranium, are also located within the brainstem. These include the trigeminal nerve (cranial nerve V); its sensory portion supplies touch, temperature, and pain sensation to the face, as well as innervates the cerebral vessels to form the trigeminovascular system (see chapter "Migraine and cluster headache"). The cerebellum functions to coordinate movements. The cerebral cortex contains areas important for motor and sensory functions, as well as association areas, which are required for more complex functions, such as language and executive function. The basal ganglia, including the substantia nigra, are responsible for the control of motor activity (see chapter "Parkinson's disease"). The limbic system supports a variety of functions including memory and emotion. It receives inputs from diverse areas of the brain; for example, the mesolimbic system, which plays important roles in reward, motivation, and addiction, is composed of projections from the midbrain to limbic areas (see chapter "Major depressive disorder"). The thalamus plays a critical relay function by mediating all motor output from and nearly all sensory input to the cortex. The hypothalamus is mainly involved in the regulation of visceral and endocrine activities with the hypothalamus and pituitary being the major hormonal regulators (see chapters "Major depressive disorder", "Rheumatoid arthritis", and "Overview" under part "Reproductive system").

Optimal brain function requires a well-regulated metabolic environment. Extracerebral

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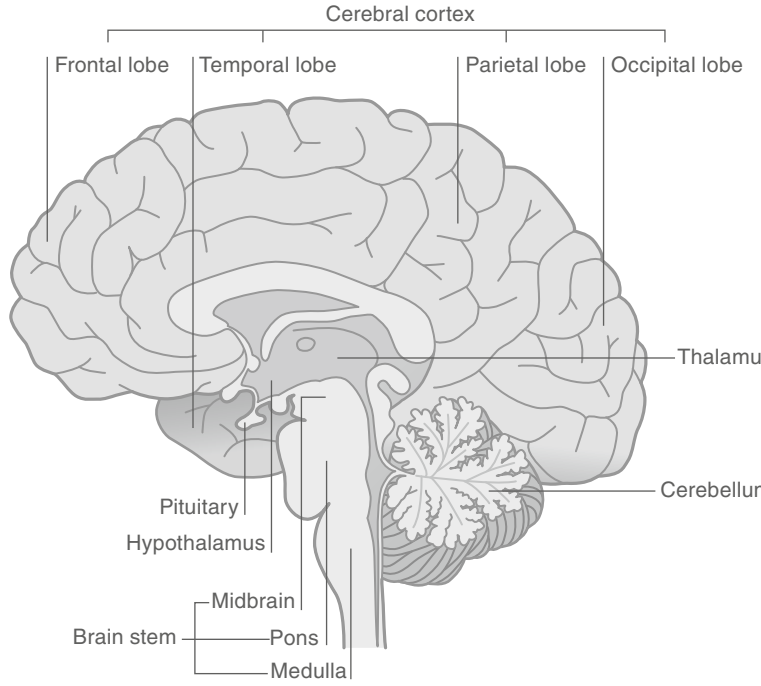

Fig. 1 Basic macroscopic anatomy of the human brain

systems remove metabolic products and protect the brain from sudden metabolic perturbations. Necessary nutrients are delivered via the circulation and must cross the blood-brain barrier (BBB), which is formed by endothelial cells lining cerebral microvessels, their basal lamina, and the end-feet of specialized glial cells called astrocytes. Astrocytes and the entire BBB protect neurons from toxic metabolites by preventing their transport into the brain via exclusion or efflux and by neutralizing harmful compounds via uptake or enzymatic inactivation [1]. Neuronal dysfunction and associated neurological diseases can occur when the brain's stable metabolic environment is disrupted.

Brain-Specific Metabolic/Molecular Pathways and Processes

Neurons are uniquely designed to receive information from the environment or other neurons, process this information, and send information to other neurons or effector tissues (i.e., neurotransmission). The cell body, or soma, contains the nucleus and additional organelles required for protein synthesis and metabolic maintenance. In most neurons, several dendrites and a single axon extend from the soma. Information is typically transported from the dendrites to the soma to the axon within a neuron by means of electrical events, which are mediated by the opening and closing of specific ion channels. Regulated transport of Na^+ and K^+ through the cell membrane is critical. Depolarization of the cell membrane occurs if positive ions (Na^+) enter the cell, whereas hyperpolarization results from exiting of positive ions (K^+) from the cell. When the cell reaches a threshold of depolarization, an electrical signal called an action potential is generated, and this signal is propagated along the length of the axon. At the axon terminal, the neuron communicates with another neuron or an effector tissue within a specialized structure called a synapse. A typical synapse consists of a presynaptic axonal bouton, a postsynaptic dendritic spine, and the intervening space called the synaptic cleft (Fig. 2). Arrival of the action potential at the axonal bouton triggers the release of neurotransmitter from presynaptic vesicles into the synaptic

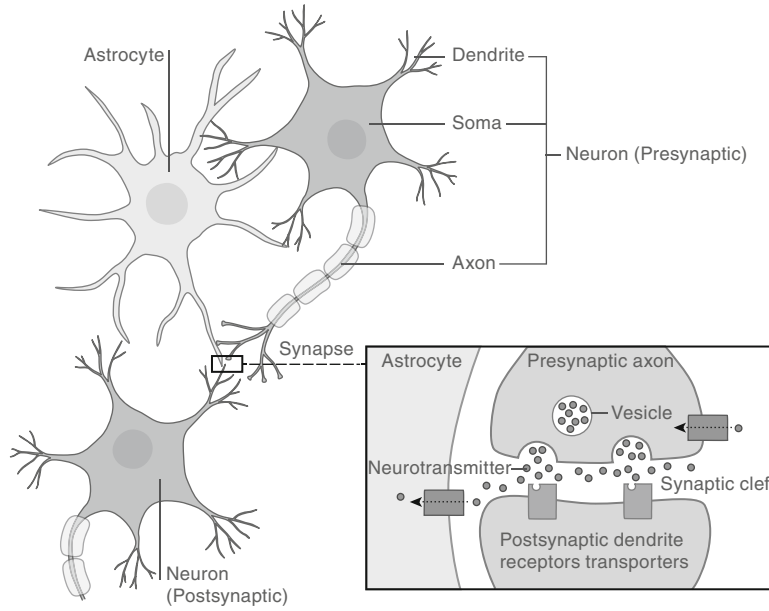

Fig. 2 Basic microscopic anatomy of the functional unit of the brain, the synapse. Neurotransmitters are cleared from the synaptic cleft by diffusion, uptake, or degradation. Postsynaptic neurotransmitter receptors are often ion channels or are associated with ion channels

cleft, thereby transforming the electrical signal into a chemical one.

A variety of molecules can act as neurotransmitters: amino acids, such as glutamate (Glu) and γ-aminobutyric acid (GABA), biogenic amines (including acetylcholine, serotonin, and the catecholamines dopamine, epinephrine, norepinephrine), nucleotides (e.g., adenosine), neuropeptides (e.g., substance P), and even gases (e.g., nitric oxide). Neurotransmitters act either directly or indirectly in controlling the opening of ion channels in the postsynaptic neuron or effector tissue (see below). They can be classified based on their effects on the postsynaptic cell; those neurotransmitters that cause depolarization are classified as excitatory, and those that cause hyperpolarization are classified as inhibitory. The major inhibitory neurotransmitter in the brain is GABA, whereas Glu represents the major excitatory neurotransmitter.

To exert their effects on the postsynaptic target, neurotransmitters first traverse the synaptic cleft and then bind to specific postsynaptic receptors. There are two major classes of receptors: ionotropic and metabotropic. Ionotropic receptors are transmembrane proteins with an intrinsic ion channel, which opens upon binding of the neurotransmitter to the receptor's extracellular domain. Metabotropic receptors do not contain their own ion channel, but neurotransmitter binding can activate intracellular signaling cascades, which produce second messengers that indirectly gate ion channels. Many neurotransmitters utilize postsynaptic receptors from both classes. As an example, Glu receptors include metabotropic Glu receptors, as well as N-methyl-D-aspartate (NMDA) receptor, AMPA receptor, and kainate receptor, which are ionotropic receptors.

The actions of neurotransmitters are terminated by their removal from the synaptic cleft (Fig. 2). Three mechanisms are involved in neurotransmitter removal: diffusion, enzymatic degradation, and reuptake into neurons or uptake into astrocytes. For example, dopamine is cleared from the synaptic cleft by dopamine transporters on the presynaptic neuron or on astrocytes and then degraded by monoamine oxidase B and catechol-O-methyltransferase. The latter also acts to degrade dopamine within the synaptic cleft (see also chapters "Major depressive disorder" and "Parkinson's disease"). Similarly, serotonin is removed from the synaptic cleft by a reuptake mechanism as well as degrading enzymes such as monoamine oxidase A (see also chapters "Major depressive disorder" and "Migraine and cluster headache").

Inside-In: Metabolites of the Brain Affecting Itself

The fundamental metabolic pathways of brain function have been uncovered studying diseases associated with inborn errors of metabolism. These inherited disorders can be classified into three major categories: (1) intoxication disorders (in which there is accumulation of toxic compounds due to a metabolic block (e.g., phenylketonuria)), (2) storage disorders due to abnormal synthesis or degradation of complex molecules (e.g., leukodystrophies), and (3) energy production disorders resulting from deficiencies in energy production or utilization (e.g., mitochondrial disorders) [2]. Because these metabolic pathways are so critical to normal brain function, perturbations due to genetic mutations often result in the manifestation of disease in the neonatal period, infancy, or childhood. However, abnormalities in any of these metabolic pathways due to genetic and/or environmental factors can also lead to neurological disorders in adults.

As an example, energy production abnormalities are common to many neurological disorders, which present in adulthood. The brain is an energy-demanding organ because the metabolic activity of neurons is high (see below). However, the brain's antioxidant capacity is relatively low, which makes it particularly susceptible to oxidative damage. Therefore, the brain is very sensitive to mitochondrial dysfunction, which leads to production of reactive oxygen species and resulting oxidative stress. This is demonstrated by the growing list of neurological diseases in which aberrations in mitochondrial function are implicated, such as Parkinson's disease (see chapter "Parkinson's disease"), Huntington's disease, and Alzheimer's disease (see chapter "Alzheimer's disease") [3].

The brain is also sensitive to aberrations in protein homeostasis, or proteostasis. Similar to other cells, neurons possess a variety of cellular systems to manage abnormal or damaging proteins. For instance, a network of interactive molecules known as the chaperone system handles misfolded proteins by refolding the proteins or directing them toward protein elimination systems including the ubiquitin-proteasome system and autophagy-lysosomal pathway [4]. Impairments in these systems can cause harmful proteins to accumulate within the intracellular or extracellular space resulting in neuronal dysfunction and death. Neurodegenerative diseases are increasingly recognized as disorders of proteostasis and thus are termed proteinopathies. Specific proteins appear to accumulate in different neurodegenerative diseases. For example, α-synuclein is implicated in Parkinson's disease (see chapter "Parkinson's disease"), β-amyloid and tau in Alzheimer's disease (see chapter "Alzheimer's disease"), and prion protein in Creutzfeldt-Jakob disease [5].

Inside-Out: Metabolites of the Brain Affecting Other Tissues

The by-products of neuronal metabolism are currently not known to directly cause disease in other organs. However, the brain indirectly influences metabolism in other parts of the body. On the one hand, the synthesis and release of hormones from the hypothalamus and pituitary regulate the endocrine system; and on the other hand, the action of neurotransmitters mediates neuronal circuits and ultimately regulates behaviors of the organism (e.g., dopamine mediates the reward system which regulates motivational behaviors; see chapter "Major depressive disorder").

The hypothalamus and pituitary are physically and functionally connected. The pituitary is composed of a posterior lobe and an anterior lobe. The supraoptic and paraventricular nuclei of the hypothalamus synthesize oxytocin and vasopressin (antidiuretic hormone), which are transported to, stored in, and released from the posterior pituitary lobe. The anterior pituitary lobe synthesizes and releases gonadotropins (which influence the gonads, see chapter "Overview" under part "Reproductive system"), thyrotropin (which influences the thyroid gland), corticotropin (which influences the adrenal glands, see chapters "Major depressive disorder", "Rheumatoid arthritis", and "Chronic kidney disease"), prolactin (which influences the mammillary glands, see

chapter "Overview" under part "Reproductive system"), and somatotropin/growth hormone (which directly influences adipocytes and the liver, see also chapters "Overview" under part "Fat tissue" and "Overview" under part "Liver"). Releasing or inhibiting hormones secreted by the hypothalamus act on the anterior pituitary gland to regulate the release of these hormones into the circulation (see also chapter "Overview" under part "Reproductive system").

One of many examples of how the action of neurotransmitters mediates neuronal circuits and thereby regulates behaviors is the dopaminergic reward system, called the mesolimbic pathway. This circuit includes dopaminergic neurons within the medial substantia nigra and ventral tegmental area of the midbrain, which connect to the nucleus accumbens/ventral striatum, as well as limbic structures such as the amygdala and hippocampus. The dopaminergic mesolimbic pathway is involved in diverse motivational behaviors including those related to appetitive and aversive motivational processes [6].

Outside-In: Metabolites of Other Tissues Affecting the Brain

The energy demand of the brain is immense and mainly satisfied by consumption of glucose. At rest, the brain accounts for 60 % of the body's glucose utilization [7]. The majority of energy consumed by the brain is used by neurons for maintenance of the membrane gradient (driving ion pumps necessary for electrical transmission), synthesis and recycling of neurotransmitters, as well as dendritic and axonal transport. Unlike most other tissues, the brain has limited fuel stores and is quite inflexible with regard to substrates for energy metabolism, deriving most of its energy from the oxidation of glucose. Thus, neurons are particularly vulnerable to disruptions in glucose availability. For example, hypoglycemia is associated with aberrations of cerebral function, which can cause an altered mental state depending on severity and duration of glucose deprivation. Hence, nutrition critically influences brain function. This is also illustrated by the use of the ketogenic diet (the second source of energy neurons are willing to accept) as treatment for epilepsy (see chapter "Epilepsy").

Metabolites of other tissues that enter the circulation must be able to cross the BBB to influence brain function. Disorders in which metabolites lead to brain malfunction resulting in altered mental status ranging from a mild confusion to coma are referred to as metabolic encephalopathies. Hypoglycemia can cause such encephalopathy (see above). Abnormalities due to dysfunction in organs such as the kidney and liver may also lead to metabolic encephalopathies. More specifically, elevated ammonia in the brain due to liver failure is a major factor involved in the pathogenesis of hepatic encephalopathy (see chapter "Cirrhosis").

Certain hormones synthesized and secreted from peripheral tissues can also cross the BBB. Most hormones exert their influence by acting on various nuclei within the hypothalamus. For example, leptin is a hormone secreted by adipocytes, which acts on the arcuate nucleus and lateral hypothalamic area to suppress appetite (see chapter "Major depressive disorder"). Gonadal hormones (e.g., estradiol, progesterone, testosterone) and adrenal hormones (e.g., cortisol) circulating in the bloodstream act on the hypothalamus to suppress their own release (negative feedback control of the hypothalamo-pituitary-gonadal and hypothalamo-pituitary-adrenal axis, respectively). Hormones are increasingly found to also have effects on neuronal function in extrahypothalamic brain areas. This is illustrated by leptin and ghrelin, two peripherally secreted peptide hormones implicated in depression (see chapter "Major depressive disorder").

Final Remarks

The brain is critical for the survival of the organism, mediating functions and behaviors that range from basic and fundamental to incredibly complex. Yet, the brain is vulnerable to perturbations or defects in metabolism. Some important associations between metabolism and brain disease will be discussed in detail in the following chapters.

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