Neuroscience of Anesthesia

From Cellular Mechanisms to Clinical Applications

Zheng Liu
Siyuan Song

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Zheng Liu • Siyuan Song

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Zheng Liu
Pathology
MD Anderson Cancer Center
Houston, TX, USA

Siyuan Song
Neuroscience
Baylor College of Medicine
Houston, TX, USA

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Preface

With the rapid advancement of science and technology and the ongoing expansion of clinical practice, the scope of modern anesthesia has significantly broadened. At its core, anesthesia involves the temporary loss of sensation—either partially or completely—through the use of drugs or other techniques, enabling conditions such as sedation, analgesia, and muscle relaxation for various medical treatments. The field now extends beyond clinical anesthesia to encompass areas such as pain management, perioperative protection of the central nervous system (CNS), and the prevention and treatment of drug addiction, among others [1, 2]. Much of anesthesia practice is intricately connected to the CNS, making a deep understanding of its structure and function essential. The foundational theories of neural structures and information transmission within the CNS, which includes the brain and spinal cord, adhere to the general principles that govern all cellular functions [2–4].

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Contents

1 Overview of Anatomy and Function of the Central Nervous System in Anesthesia

The central nervous system (CNS), comprising the brain and spinal cord, is distinct from the peripheral nervous system, which includes all other neural elements.

The brain, safeguarded by the skull, meninges, and cerebrospinal fluid, is the central organ responsible for responses, sensations, movement, emotions, communication, thought processing, and memory. It is divided into four main regions: the cerebrum, diencephalon, brainstem, and cerebellum. Additionally, the blood-brain barrier, which surrounds and protects the brain's blood vessels, acts as a selective shield, preventing harmful substances in the bloodstream from entering the brain [1, 2].

The spinal cord, located within the vertebral column, consists of gray matter containing nerve cells and white matter with ascending and descending tracts. It plays a crucial role in transmitting motor commands from the brain to the peripheral body and relaying sensory information from sensory organs to the brain. Like the brain, the spinal cord is protected by bone, meninges, and cerebrospinal fluid. Understanding the anatomy and function of the CNS is fundamental to comprehending how anesthetics affect neural pathways and overall nervous system functioning [1].

1.1 Brain

The brain is a paramount organ of the human body, housed securely within the bony cranial cavity. Its weight ranges from 1200 g to 1500 g, with the average adult male brain weighing about 1370 g and the average adult female brain around 1200 g [3]. The brain not only regulates itself but also controls all other body systems, ensuring the harmonious operation of internal organs. It is structurally and functionally intricate, primarily divided into the cerebrum, cerebellum, and brainstem. The brain also boasts a rich vascular network and a ventricular system filled with cerebrospinal fluid (CSF) (Fig. 1.1).

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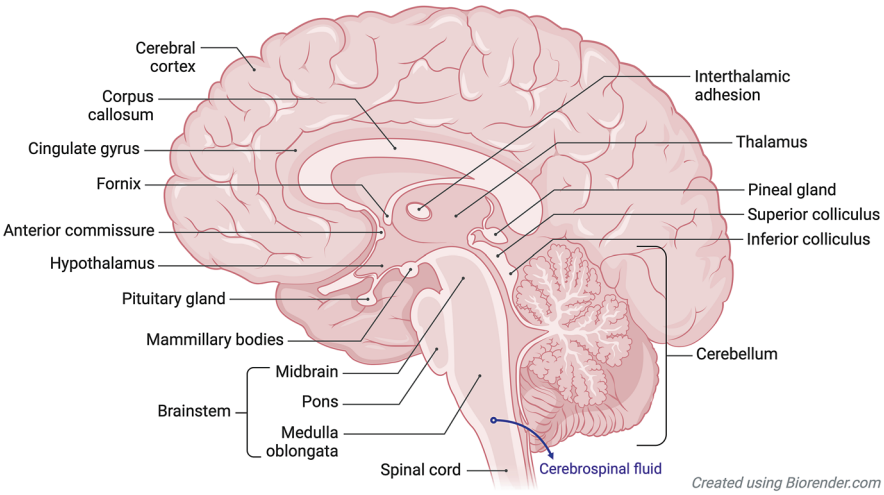

Fig. 1.1 Schematic diagram of brain anatomy

1.1.1 Cerebrum

The cerebrum, the largest part of the brain, is composed of the left and right cerebral hemispheres, which are interconnected by the corpus callosum. These hemispheres are highly developed and cover the diencephalon, midbrain, and cerebellum. The cerebral cortex, which forms the brain's outermost layer of nerve tissue, constitutes about 40% of the brain's weight (around 600 g) and spans an area of approximately 2200 cm^2 [4]. Each hemisphere is divided into four distinct lobes: frontal, temporal, parietal, and occipital [5]. The cortex features grooves (sulci) and raised areas (gyri), each associated with specific functions [6].

Key Sulci and Their Functions

- **Central sulcus:** Separates the frontal lobe from the parietal lobe and divides motor functions (precentral gyrus) from sensory functions (postcentral gyrus) [6].
- **Lateral sulcus (Sylvian fissure):** Divides the temporal lobe from the frontal and parietal lobes; it is involved in speech and auditory processing areas [6].
- **Calcarine sulcus:** Found in the occipital lobe, it contains the primary visual cortex and is essential for vision processing [6].

Key Gyri and Their Functions

- **Precentral gyrus**: Manages voluntary motor functions [7]
- **Postcentral gyrus**: Handles sensory functions, including touch, proprioception, and pain/temperature [7]

- **Superior temporal gyrus:** Involved in auditory processing and language comprehension (Wernicke's area) [8]
- **Transverse temporal gyrus**: Responsible for primary auditory processing [8]
- **Hippocampal gyrus (parahippocampal gyrus)**: Plays a role in memory formation and spatial navigation and is linked to smell (via the entorhinal cortex) and taste [8]
- **Lingual gyrus and cuneus**: Responsible for visual processing (Fig. 1.2) [8]

Motor and sensory functions are lateralized, with each hemisphere controlling the opposite side of the body, i.e., the left hemisphere controls the right side of the body and vice versa; meanwhile, hearing, smell, taste, and vision are controlled by both hemispheres. The two cerebral hemispheres appear symmetrical but are not mirror images. Typically, the left hemisphere dominates in language and analytical thinking, while the right hemisphere is more involved with spatial awareness and emotional processing [9].

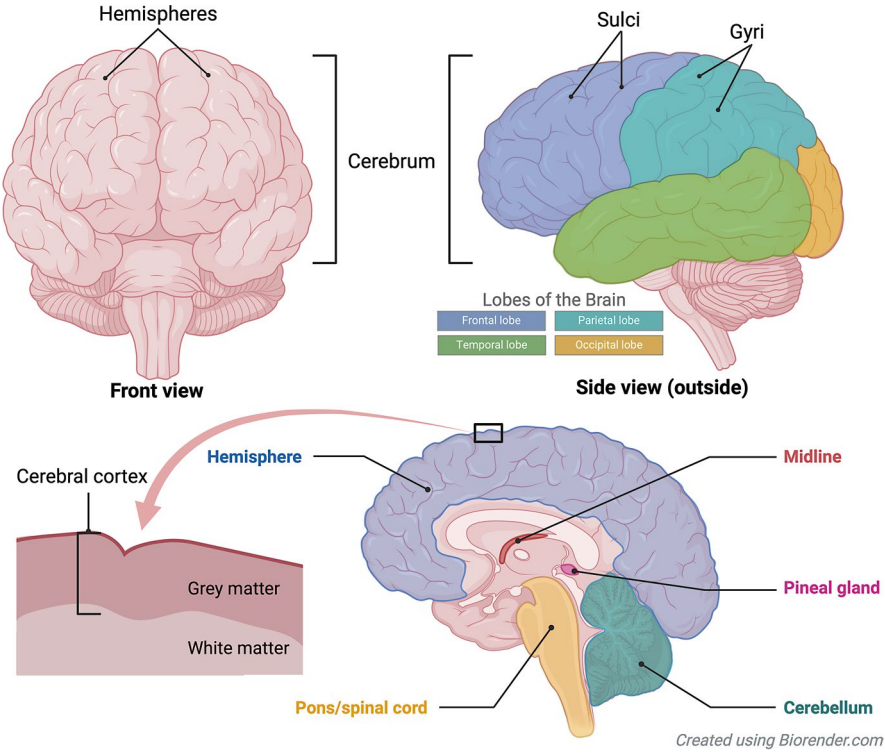

Fig. 1.2 Anatomy of the cerebral cortex

- **Frontal Lobe**
  Situated anterior to the central sulcus, the frontal lobe is key for voluntary motor activity, problem-solving, attention, memory, and language. It contains the motor cortex, which coordinates precise voluntary movements of skeletal muscles, and Broca's area, which is crucial for speech production.
- **Parietal Lobe**
  Located behind the central sulcus and separated from the occipital lobe by the parieto-occipital sulcus, the parietal lobe processes sensory information through the somatosensory cortex. Neurons here receive sensory input from the body, facilitating the perception of touch and spatial orientation.
- **Occipital Lobe**
  The occipital lobe serves as the visual processing center, housing the visual cortex. It interprets signals from the retina using past visual experiences to aid in recognizing stimuli.
- **Temporal Lobe**
  This lobe processes auditory information through the auditory cortex. Wernicke's area, located within the temporal lobe, is essential for understanding spoken language.
- **Basal Ganglia**
  Deep within the cerebral white matter are the basal ganglia, comprising the caudate nucleus, putamen, and globus pallidus. These structures, collectively forming the pallidum and striatum, play a critical role in regulating muscle movements and coordination.

1.1.2 Diencephalon

Located deep in the brain, the diencephalon contains several key structures [10]:

- **Thalamus**: Acts as the brain's relay center, processing sensory inputs and distributing them to appropriate cortical areas. It also influences consciousness and sleep.
- **Hypothalamus**: Essential for homeostasis, it links the CNS to the endocrine system and regulates heart rate, blood pressure, appetite, thirst, temperature, and hormone release via the pituitary gland.
- **Epithalamus**: Comprising the pineal gland and habenular nuclei, the epithalamus is involved in the regulation of circadian rhythms and the secretion of melatonin. The habenular nuclei play a role in emotional and reproductive behaviors.
- **Subthalamus**: Located below the thalamus, it includes the subthalamic nucleus, which is crucial for the regulation of motor functions. It interacts with the basal ganglia to control movements and is involved in motor planning and execution.
- **Metathalamus**: This region consists of the medial and lateral geniculate bodies. The medial geniculate body is part of the auditory pathway, processing and relaying auditory information to the auditory cortex. The lateral geniculate body is part of the visual pathway, relaying visual information from the retina to the visual cortex.

1.1.3 Cerebellum

Situated on the dorsal side of the pons and medulla, the cerebellum is covered by the cerebellar tentorium. It ensures smooth, coordinated voluntary movements and balance. The cerebellum comprises the central vermis and two lateral hemispheres, containing nuclei such as the dentate, fastigial, emboliform, and globose [11]. It processes higher-level instructions from the cerebral cortex and sends messages to the motor cortex for muscle coordination, with each side controlling the same side of the body, i.e., the right side controls the right side, and the left side controls the left side. The cerebellar tonsil, located at its lower part, can herniate under high intracranial pressure [12].

1.1.4 Brainstem

Located in the posterior cranial fossa, the brainstem connects the diencephalon above to the spinal cord below. It consists of the midbrain, pons, and medulla and contains neural nuclei, tracts, and the reticular formation [13].

- **Brainstem Neural Nuclei**
  These gray matter nuclei are distributed within the brainstem:
  1. **Midbrain**: Contains nuclei for cranial nerves III and IV.
  2. **Pons**: Houses nuclei for cranial nerves V, VI, VII, and VIII.
  3. **Medulla**: Contains nuclei for cranial nerves IX, X, XI, and XII, along with relay nuclei for deep sensation and extrapyramidal system nuclei like the red nucleus and substantia nigra.
- **Brainstem Tracts**
  These white matter tracts include deep and superficial sensory, corticospinal, extrapyramidal tracts, and the medial longitudinal fasciculus.
- **Reticular Formation**
  The reticular formation, a complex network of neuronal cell bodies and fibers in the brainstem, has extensive connections to various brain regions. It contains critical regulatory centers essential for maintaining normal physiological functions such as cardiovascular regulation, blood pressure control, respiration, and vomiting. Some nuclei within the reticular formation gather and transmit diverse information to the thalamus, which then relays it to extensive areas of the cerebral cortex. This transmission is crucial for sustaining consciousness, forming the basis of the ascending reticular activating system. Damage to this network can result in significant disturbances in consciousness.

1.1.5 Brain Blood Vessels

The brain requires a substantial blood supply, consuming about 20% of the body's total blood flow despite making up only 2% of body weight. This makes the brain

highly dependent on a continuous blood supply and extremely sensitive to hypoxia. The arterial walls in the brain are characterized by their thinness, while the venous walls lack smooth muscle and the veins are valveless, forming unique dural sinuses. Unlike arteries, veins in the brain do not accompany the arteries but instead form their distinct paths, resulting in unique dural sinuses. The presence of blood-brain barriers adds to the clinical significance of these structures [14].

1.1.6 Ventricles and Cerebrospinal Fluid

The brain's intrinsic cavities, known as ventricles, include the fourth, third, and lateral ventricles, all of which are filled with cerebrospinal fluid (CSF). In adults, the CSF volume typically ranges from 140 ml to 180 ml, with 30 ml to 40 ml in the lateral ventricles, 25 ml to 30 ml in the third and fourth ventricles, 55 ml to 65 ml in the subarachnoid space, 10 ml to 15 ml in the spinal subarachnoid space, and 20 ml to 30 ml in the terminal cistern. The daily production of CSF is approximately 500 ml to 600 ml, with an equivalent amount absorbed back into the bloodstream, indicating a high turnover rate. CSF is mainly secreted by the choroid plexuses in the lateral, third, and fourth ventricles, flowing through the third ventricle via the interventricular foramen, then through the fourth ventricle via the aqueduct of Sylvius, and into the subarachnoid space. Besides the choroid plexuses, ependymal cells also contribute to CSF secretion. Fluid filtered from the blood vessels of the pia mater and brain capillaries is partly reabsorbed, with the rest entering the subarachnoid space surrounding the vessels and becoming part of the CSF. CSF is absorbed into the venous blood through arachnoid villi, which contain microtubules with diameters of 4 μm to 12 μm. When the pressure in the subarachnoid space exceeds that in the venous sinuses, these microtubules open, allowing CSF and small particles like proteins and red blood cells to enter the venous blood. When the subarachnoid space pressure is lower than the venous sinuses pressure, the microtubules close, preventing backflow. CSF pressure, averaging 1.3 kPa (10 mmHg) in a normal lateral position, is crucial for cerebral blood flow and brain function. When CSF absorption is obstructed, increased pressure affects brain function. The primary functions of CSF include cushioning the brain, spinal cord, cranial cavity, and spinal canal, providing protective significance. The brain, immersed in CSF, is buoyed, reducing its effective weight to about 50 g. CSF, secreted by the choroid plexuses, flows through the ventricular system into the subarachnoid space and is absorbed into venous blood via arachnoid villi. This process cushions the brain and spinal cord, reduces the brain's effective weight, and facilitates substance exchange between the brain and blood [15].

1.1.7 Brain Barriers

Stable neuronal function in the CNS requires a controlled environment. This stability is maintained by selective permeability of substances between the blood and brain/spinal fluid, forming what are known as brain barriers:

- **Blood-Cerebrospinal Fluid Barrier.**
  The CSF, primarily produced by the choroid plexuses, has a composition distinct from plasma, reflecting active transport processes. It contains very low protein content and lower glucose levels than plasma but higher concentrations of sodium (Na^+), magnesium (Mg^{2+}), and lower concentrations of potassium (K^+), bicarbonate (HCO_3^-), and calcium (Ca^{2+}) compared to plasma. This indicates active transport of substances between the blood and CSF. Large molecules struggle to cross this barrier, characterized by non-fenestrated capillary walls and specialized carrier systems, forming the blood-cerebrospinal fluid barrier. The permeability of this barrier varies; lipid-soluble substances like oxygen (O_2) and carbon dioxide (CO_2) pass easily, while many ions have low permeability.
- **Blood-Brain Barrier**
  This barrier restricts the exchange of substances between the blood and brain tissue. Lipid-soluble substances such as O_2, CO_2, certain anesthetics, and ethanol cross easily, whereas water-soluble substances show variable permeability. For example, glucose and amino acids pass through readily, while mannitol and sucrose exhibit very low permeability or none at all. This differential permeability suggests an active transport process distinct from other body capillaries. Electron microscopy reveals that most brain capillaries are surrounded by astrocytic processes known as perivascular feet. The blood-brain barrier's structure includes endothelial cells, the basement membrane, and the perivascular feet of astrocytes. This specific permeability to various substances is vital for its function [16].
- **Cerebrospinal Fluid-Brain Barrier**
  The barrier between CSF in the ventricles or subarachnoid space and neural tissue is formed by the ependymal epithelium or pia mater and the subpial glial membrane. This structure restricts the diffusion of large molecules between the CSF and brain parenchyma via tight and gap junctions [17].

1.2 Spinal Cord

The spinal cord, a slightly flattened cylindrical structure, resides within the vertebral canal and extends downward from the brainstem. It consists of gray matter, which houses nerve cells, and white matter, which contains ascending and descending tracts. The spinal cord is the origin of 31 pairs of spinal nerves that extend to the limbs and trunk; its normal functions are regulated by the brain [18] (Fig. 1.3).

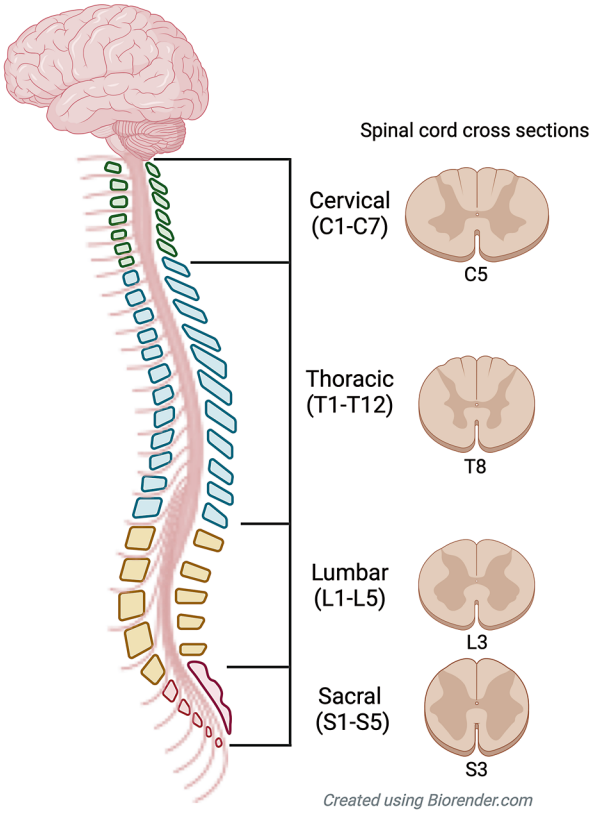

Fig. 1.3 Regional organization of the human spinal cord with corresponding cross sections

1.2.1 External Structure of the Spinal Cord

The spinal cord, a central part of the nervous system, extends downward from the brainstem, measuring between 42 cm and 45 cm in length. It connects to the medulla at the foramen magnum at its upper end and terminates at the lower edge of the first lumbar vertebra at its lower end, occupying the upper two-thirds of the vertebral canal. It gives rise to 31 pairs of spinal nerves corresponding to 31 segments: eight cervical (C1–C8), 12 thoracic (T1–T12), five lumbar (L1–L5), five sacral (S1–S5), and one coccygeal (Co). Each segment has two pairs of nerve roots—anterior (ventral) and posterior (dorsal) [19].

During development, the spinal cord grows more slowly than the vertebral column, resulting in a shorter spinal cord in adults, with its lower end positioned higher than the corresponding vertebrae. Cervical segments are one vertebra higher, upper and middle thoracic segments are two vertebrae higher, and lower thoracic segments are three vertebrae higher. Lumbar segments are situated between the tenth and 12th thoracic vertebrae, while sacral segments are located at the level of the 12th thoracic

vertebra and the first lumbar vertebra. Due to the differential growth rates, the nerve roots from the lower segments of the spinal cord slope downward more steeply. The lumbar nerve roots descend almost vertically, forming the cauda equina, comprising ten pairs of nerve roots from L2 to the coccygeal segment.

The spinal cord, slightly flattened and cylindrical, varies in thickness along its length. It has two enlargements: the cervical enlargement (C5 to T2), from which nerve roots to the upper limbs arise, and the lumbar enlargement (L1 to S2), from which nerve roots to the lower limbs arise. Below the lumbar enlargement, the spinal cord tapers to form the conus medullaris, with its apex giving off the filum terminale, terminating at the periosteum of the first coccygeal vertebra [20].

The surface of the spinal cord features six longitudinal grooves: the anterior median fissure, which is deep and extends into one-third of the anteroposterior diameter of the spinal cord, and the posterior median sulcus, which divides the posterior funiculus into symmetrical left and right parts. Additionally, there are anterior lateral sulci and posterior lateral sulci on each side. Anterior nerve roots exit the spinal cord through the anterior lateral sulci, while posterior nerve roots enter through the posterior lateral sulci [21].

The spinal meninges, mirroring the brain meninges, comprise three layers: the outermost dura mater (a continuation of the cranial dura mater), which forms a blind end at the sacral segments. Beneath the dura mater is the thin, transparent arachnoid membrane, followed by the innermost vascular pia mater, which closely envelops the spinal cord. The space between the dura mater and vertebral periosteum, known as the epidural space, contains venous plexuses and fat tissue [22]. The subdural space, situated between the dura mater and the arachnoid membrane, lacks specialized structures. The subarachnoid space, filled with cerebrospinal fluid (CSF), lies between the arachnoid membrane and the pia mater, continuing into the subarachnoid space of the brain. Spinal nerves pass through the arachnoid membrane and attach to the inner surface of the dura mater as denticulate ligaments, which stabilize the spinal cord.

1.2.2 Internal Structure of the Spinal Cord

The spinal cord comprises gray matter and white matter. Gray matter, grayish red in appearance, consists mainly of nerve cell nuclei and neuroglial cells, forming a butterfly or "H" shape in the center of the spinal cord's cross section, with a central canal at its core. White matter, surrounding the gray matter, consists predominantly of ascending and descending tracts and numerous glial cells [23].

- **Gray Matter**
  The gray matter is divided into the anterior horn, posterior horn, and lateral horn (in segments C8–L2 and S2–4). It also includes the gray commissures, located anterior and posterior to the central canal, together forming the central gray matter. The gray matter contains various nerve cells of different sizes, shapes, and functions, which are critical for receiving and transmitting impulses. The

anterior horn primarily controls trunk and limb movements; the posterior horn relays sensory information; the lateral horn from C8–L2 serves as the spinal cord's sympathetic center regulating blood vessels, internal organs, and glands; and the lateral horn from S2–4 serves as the parasympathetic center regulating the bladder, rectum, and sexual organs.

- **White Matter**
  The white matter is divided into the anterior funiculus, lateral funiculus, and posterior funiculus. The anterior funiculus lies medial to the anterior horn and root, the lateral funiculus between the anterior and posterior horns, and the posterior funiculus between the posterior median sulcus and the posterior horn and root. Additionally, there is an anterior white commissure in front of the gray commissure and a reticular formation in the basal part of the posterior horn, where gray and white matter intermingle. The white matter consists mainly of ascending (sensory) and descending (motor) tracts and numerous glial cells. The ascending tracts convey various sensory information to the brain, while the descending tracts transmit neural impulses from different brain regions to the spinal cord [23].

1.2.3 Ascending Tracts

Also known as sensory tracts, these transmit pain, temperature, fine touch, and proprioception from the trunk and limbs to the brain's sensory cortex for processing and integration. Key tracts include:

- **Gracile and cuneate fasciculi:** Located in the posterior funiculus, these tracts conduct proprioception and fine touch from muscles, tendons, and joints to the gracile and cuneate nuclei in the medulla and then to the brain cortex.
- **Spinocerebellar tracts:** Divided into anterior and posterior tracts, situated in the anterior and posterior parts of the lateral funiculus, they transmit deep sensory information from the lower limbs and trunk to the cerebellar cortex via the superior and inferior cerebellar peduncles, aiding in movement and posture regulation.
- **Spinothalamic tracts:** Comprising lateral and anterior spinothalamic tracts, located in the anterior part of the lateral funiculus and the anterior funiculus, respectively. These tracts relay information from the posterior roots to the ventral posterolateral nucleus of the thalamus and then to the postcentral gyrus and paracentral lobule for integration, forming a crucial part of the sensory conduction pathway.

1.2.4 Descending Tracts

Known as motor tracts, these convey impulses from the motor cortex, red nucleus, vestibular nucleus, reticular formation, and superior colliculus to the anterior and lateral horns of the spinal cord. They control trunk and limb muscles, contributing

to the formation of the pyramidal and extrapyramidal systems and involving voluntary movement, posture, and balance. Major tracts include corticospinal tracts, rubrospinal tracts, vestibulospinal tracts, reticulospinal tracts, tectospinal tracts, and the medial longitudinal fasciculus.

1.2.5 Blood Supply of the Spinal Cord

- **Arteries of the Spinal Cord**
  The spinal cord receives its blood supply from the anterior and posterior spinal arteries, branches of the vertebral arteries, and radicular arteries. The vertebral arteries, descending continuously reinforced by radicular arteries, collectively supply blood to the spinal cord. Areas with the least circulation are often at the junctions of adjacent radicular artery distribution areas, with T4 and L1 being most prone to insufficient blood supply [24].
- **Veins of the Spinal Cord**
  The spinal veins mainly drain into the vertebral venous plexus via the anterior and posterior spinal veins. This plexus connects upward with the medullary veins, with the azygos vein and superior vena cava in the thoracic region, and with the inferior vena cava, portal vein, and pelvic veins in the abdominal region. The vertebral venous plexus lacks valves, and its low pressure allows blood flow direction to change with variations in thoracic and abdominal pressures, potentially serving as pathways for infections and malignant tumors to spread to the cranium [25].

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Neurons in Anesthesia and Pain Regulation

2

The central nervous system (CNS) is fundamentally composed of two critical cell types: neurons and neuroglial cells. Both play essential roles in anesthesia and the body's vital activities. Anesthetic and analgesic drugs exert their effects through these cells, enabling anesthesia and pain relief. The CNS forms a complex three-dimensional structure through the precise organization of these cells, with neurons and glial cells being distinct in their structure, chemistry, and functions. The adult brain, weighing around 1300 g, contains about 100 billion neurons, with the number of glial cells being roughly ten times greater. While glial cells are more abundant, neurons are crucial for the brain's unique functions [1].

Neurons can be categorized into sensory neurons, interneurons, and motor neurons. Sensory neurons detect internal and external changes and transmit this information to the CNS's most complex neurons, the interneurons. Interneurons process and store sensory information, relaying instructions to motor neurons, which then command effectors (muscle or gland cells) to respond to stimuli. Neuroglia, in contrast, insulate, support, and nourish neurons. Despite the significant role of glial cells, neurons are primarily responsible for information processing in the brain, thus receiving the most attention [2].

2.1 Morphology and Structure

Neurons are the fundamental structural and functional units of the nervous system. The journey toward fully understanding neurons has been both long and complex, beginning in the late seventeenth century. However, significant breakthroughs occurred with the invention of the microscope, as well as the development of tissue fixation and staining techniques, which allowed for more detailed studies of neuronal structures. These advancements ultimately culminated in the neuron theory proposed by Santiago Ramón y Cajal, which established neurons as the essential building blocks of the nervous system's structure and function. Each neuron is composed of a soma (cell body), along with extensions known as dendrites and axons,

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which enable communication with other neurons, thus supporting the overall neural network (Fig. 2.1) [3].

2.1.1 Neuron Classification

The classification of neurons is intricate due to their vast diversity. Neurons can be categorized based on various criteria, including the number of processes they possess, their connectivity patterns, axon length, and the type of neurotransmitter they release. Understanding these classifications aids in comprehending the varied roles and functions of different neurons within the nervous system [4].

- **Classification Based on the Number of Processes**
  - **Unipolar neurons:** These neurons have a single process extending from the cell body.
  - **Bipolar neurons:** These neurons feature two distinct processes.
  - **Multipolar neurons:** These neurons possess three or more processes, making them the most common type of neuron.
- **Classification Based on Connectivity**
  - **Primary sensory neurons**: These neurons convey information from sensory receptors to the central nervous system.
  - **Motor neurons**: These neurons connect to muscles and control their movements.
  - **Interneurons**: These neurons form connections exclusively with other neurons and are the most abundant and intricate within the CNS.
- **Classification Based on Axon Length**
  - **Golgi type I neurons (projection neurons)**: Characterized by long axons that extend far beyond the cell body.

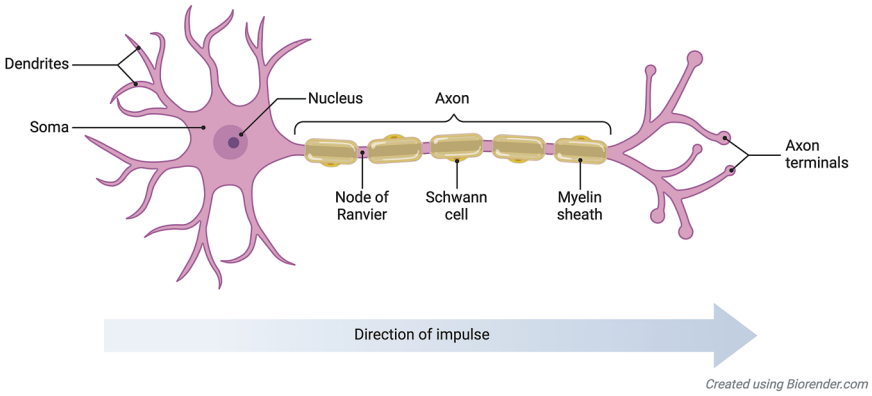

Fig. 2.1 Morphology and structure of neurons

  - **Golgi type II neurons:** These neurons have short axons that do not extend beyond their dendritic range, i.e., the stellate cells found in the cerebral cortex.
- **Classification Based on Neurotransmitters**
  - Neurons can be classified chemically based on the neurotransmitters they contain. For example, motor neurons that release acetylcholine are classified as cholinergic neurons. Neurons containing monoamine neurotransmitters (such as norepinephrine, dopamine, and serotonin) are classified as monoaminergic neurons.

2.1.2 Structure of Neurons

- **Cell Body (Soma)**

The soma, or cell body, is the spherical central region of a neuron, typically measuring around 20 μm in diameter. It is filled with cytosol, a potassium-rich aqueous solution. The cell membrane, approximately 5 nm thick, delineates the interior of the cell from its external environment. Within the soma are various organelles, including the rough and smooth endoplasmic reticulum, the Golgi apparatus, and mitochondria. All the components within the cell membrane, excluding the nucleus, are referred to collectively as the cytoplasm. The nucleus contains Nissl substance, composed of rough endoplasmic reticulum and free ribosomes, which varies across different neuron types [5].

- **Dendrites**

Dendrites are branched extensions emanating from the soma, resembling tree branches. The ensemble of dendrites from a single neuron is termed a dendritic tree. The shape and size of these trees vary significantly among different neuron types, aiding in their classification. Dendrites serve as the primary receivers of synaptic inputs from other neurons, hosting numerous synapses. Their postsynaptic membranes are equipped with receptors that capture neurotransmitter signals from the synaptic cleft [5].

- **Axon**

Axons are specialized structures designed for long-distance signal transmission within the nervous system. They consist of several key components: the axon hillock, the initial segment, the axon proper, and the terminals. The axon hillock is a cone-shaped area around the soma where the axon originates. The initial segment extends from the axon hillock to the beginning of the myelin sheath. The myelin sheath, formed by oligodendrocytes in the CNS and Schwann cells in the peripheral nervous system, insulates the axon, facilitating rapid signal conduction. The gaps in the myelin sheath, known as nodes of Ranvier, are critical for the propagation of action potentials [5].

2.2 Synapses and Plasticity

Synapses are specialized junctions where neurons communicate with each other, which was proposed first in 1897 by Sherrington [6]. They derive their name from the Greek word meaning "to clasp" [7, 8]. These structures are vital for neuronal communication and can be classified as either electrical or chemical, depending on their mode of transmission. Electrical synapses allow for the rapid transmission of signals through direct diffusion of action potentials, with almost no delay. In contrast, chemical synapses rely on neurotransmitters to transmit signals between neurons. This section will specifically discuss chemical synaptic transmission. Chemical synapses are highly sensitive to chemical influences and are key targets for various general anesthetics. Central synaptic plasticity is crucial for brain functions like learning and memory, making it important to understand how general anesthetics affect it. Synaptic plasticity generally includes changes in synaptic transmission, synaptic development, and synaptic morphology, typically referring to synaptic transmission plasticity unless otherwise noted. Research on synaptic plasticity is one of the fastest-growing fields in neuroscience [9–12].

2.2.1 Chemical Synapses

Chemical synapses are intricate junctions that consist of three primary components: the presynaptic region, the synaptic cleft, and the postsynaptic region (refer to Fig. 2.2 for a detailed structure) [13]. The presynaptic area, typically 1–2 μm in diameter, includes the presynaptic membrane, synaptic vesicles, microtubules, mitochondria, multivesicular bodies, and several nerve filaments that terminate within the presynaptic region but remain distant from the membrane, with microtubules extending close to the membrane [14]. The synaptic cleft, spanning 20–40 nm, lies between the presynaptic and postsynaptic membranes and contains cross-plates formed by an electron-dense intercellular matrix, with vertical filaments linking the pre- and postsynaptic membranes. This cleft is rich in sialic acid, glycoproteins, and neural cell adhesion molecules. The postsynaptic region comprises the postsynaptic membrane, subsynaptic reticulum, postsynaptic density, and mitochondria. The postsynaptic membrane, a part of the neuron's cell membrane, is characterized by a dense layer formed by closely attached dense substances on its cytoplasmic side, housing various receptors and ion channels critical for synaptic function [15, 16].

Chemical synapses operate primarily through the release of neurotransmitters and modulators from synaptic vesicles in the presynaptic component. Synaptic vesicles, typically 40–50 nm in diameter, vary in size and shape. They are categorized based on their shape and chemical content into:

- **Clear vesicles:** Contain neurotransmitters like acetylcholine, GABA, or glycine [17]
- **Granulated vesicles with dense cores:** Contain monoamines such as catecholamines and serotonin [18]

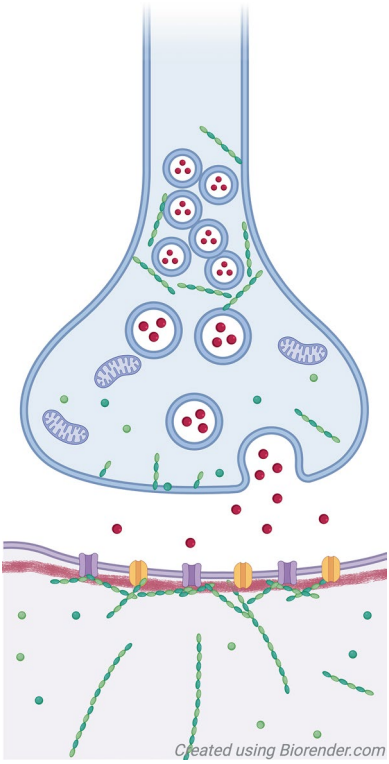

Fig. 2.2 Diagram of synapse structure (as indicated by arrows)

Depending on the connection components, chemical synapses are further classified into axodendritic, axosomatic, axoaxonic, and dendrodendritic synapses [19]. At the ultrastructural level, synapses are classified into type I and type II. Type I synapses, with a thicker and denser postsynaptic membrane, are asymmetrical and mainly excitatory, typically involving monoamines. In contrast, type II synapses are symmetrical and primarily inhibitory, involving neurotransmitters like GABA or glycine [20].

Chemical synapses exhibit several functional characteristics [21, 22]:

- Unidirectional transmission
- Synaptic delay
- Summation
- Fatigability
- Sensitivity to environmental factors

2.2.2 Electrical Synapses

Electrical synapses facilitate signal transmission through direct electrical coupling, allowing signals to pass swiftly to the next neuron with minimal or no synaptic

delay. These signals can be transmitted bidirectionally and are always excitatory. At the ultrastructural level, electrical synapses are symmetrical, characterized by a very narrow synaptic cleft of about 2 nm, forming a gap junction that provides a low-resistance pathway for ions between adjacent cells, enabling the easy passage of electrical currents [23]. While vesicle-like structures may occasionally be observed in electrical synapses, physiological and biochemical studies have not confirmed any chemical transmission characteristics for these vesicles [24].

2.2.3 Synaptic Plasticity in the Central Nervous System

Synaptic plasticity refers to the ability of synapses to undergo relatively long-lasting changes in morphology and function. Physiologically, synaptic plasticity primarily denotes changes in synaptic transmission efficiency. Ubiquitous in the central nervous system (CNS), synaptic plasticity is closely linked to the development of immature nervous systems and advanced brain functions such as learning and memory [25]. Major forms of synaptic plasticity include:

- **Post-tetanic potentiation (PTP)**:
  PTP refers to the transient enhancement of synaptic transmission following repetitive presynaptic stimulation. This short-term increase in postsynaptic potential amplitude is thought to result from a buildup of intracellular calcium in the presynaptic terminal, facilitating neurotransmitter release. PTP may play a role in modulating synaptic responsiveness during periods of heightened neural activity, potentially relevant in the context of anesthetic modulation.
- **Habituation and sensitization**:
  Habituation is characterized by a progressive decline in neural response following repeated exposure to a nonthreatening stimulus, reflecting a form of synaptic depression. Conversely, sensitization involves an amplified and prolonged response to a previously encountered stimulus, typically following a noxious or significant event. Both processes are essential for adaptive neural function and may be influenced by anesthetic agents, which can either attenuate or enhance these synaptic plasticity mechanisms depending on the context.
- **Long-term potentiation (LTP) and long-term depression (LTD)**:
  LTP is a long-lasting enhancement in synaptic strength resulting from high-frequency stimulation of presynaptic neurons, which increases the efficacy of synaptic transmission in postsynaptic neurons. LTD, in contrast, results from low-frequency stimulation, leading to a sustained decrease in synaptic strength. Both LTP and LTD are key mechanisms underlying synaptic plasticity and memory formation, and their modulation by anesthetic agents may contribute to alterations in cognitive function and neural plasticity during and after anesthesia [26].

2.2.4 Synaptic Plasticity and Pain

The exploration into the link between synaptic plasticity and pain began gaining traction in the early 1990s. Randic and colleagues were pioneers in this field, initially demonstrating in vitro that particular frequencies of presynaptic stimulation could evoke LTP in synaptic transmission between dorsal root nociceptive fibers and sensory neurons in the spinal dorsal horn [27]. Subsequent in vivo experiments revealed that high-frequency stimulation of the sciatic nerve could induce LTP of field potentials triggered by C-fibers in the spinal dorsal horn. Conversely, low-frequency stimulation of another type of nociceptive sensory fiber, Aδ fibers, was found to induce LTD in their synaptic transmission with sensory neurons in the spinal dorsal horn, reliant on intracellular calcium in the postsynaptic neuron [28]. Further investigations uncovered that LTP and LTD in the spinal dorsal horn are linked to various receptors and ion channels, many of which are also involved in hippocampal LTP/LTD, indicating that learning, memory, and pain share common underlying mechanisms [29]. The phenomenon of synaptic plasticity within the pain system offers valuable insights into pain modulation and significantly enhances the classical "gate control" theory proposed in the 1960s.

2.3 Neural Circuits

Neurons that regulate anesthesia and pain operate mainly through diverse neural circuits or networks composed of various neurons. These networks process and integrate extensive and complex information. In neural circuits, synapses are the primary sites for information transmission. A neuron's dendrites or soma can receive numerous synaptic contacts from multiple axon terminals, originating from one or more neurons. This mode, where multiple sources of information converge on a single neuron, is termed convergence. Conversely, a single neuron can form synaptic contacts with multiple other neurons, amplifying the information in a mode called divergence [30]. The CNS features various forms of divergence and convergence, leading to the diffusion or aggregation of information processing, and overlapping temporal and spatial patterns. These form intricate neural networks, refining information processing and integration and making regulatory activities more precise, coordinated, and harmonious. The dendrites and axons of neurons can form synaptic contacts with different parts of other neurons, creating microcircuits with specific functions [31].

The CNS contains numerous interneurons with short processes and small somas. In the human brain, interneurons account for about 99% of the total neuron population. These interneurons are integral to local neural circuits within or between brain nuclei. They play a crucial role in CNS activities, with the complexity of these activities largely determined by the diversity of neural circuits. The same incoming information can be transmitted to various central brain levels through different pathways and to effectors via multiple routes. Many interneurons form complex, multifaceted local neural circuits with neurons of long projection systems, deeply

processing and continuously modulating transmitted information. Although the basic forms of neural circuit processing at different levels may be similar, the relative importance of information processing at various levels or hierarchies and the interactions between circuits can vary, making the regulation of neural activities more complex [9].

2.3.1 Neural Circuits of General Anesthesia

During anesthesia, neuronal activity in certain brain regions increases, and the activity of nuclei shows spatiotemporal differences under different states of anesthesia. These nuclei are distributed across the brainstem, hypothalamus, thalamus, and other regions. Through various neurotransmitters, they regulate each other, forming a complex network that collectively controls the input and communication of cortical information. Presently, three main neural circuits are believed to be closely related to anesthesia and consciousness: thalamocortical circuits, hypothalamic sleep-wake circuits, and cortical fragmentation circuits [32].

- **Thalamocortical Circuits**

The thalamus serves as a common pathway for ascending activation systems and descending facilitation pathways and acts as a relay station for cortex-cortex neural pathways. It also has extensive connections with hypothalamic nuclei, making it a convergence point for multiple neural networks. Under anesthesia, thalamic function is inhibited, which limits the information processing capacity of the thalamocortical circuits and blocks peripheral information transmission to the cortex, potentially explaining the reversible loss of consciousness induced by anesthesia [33].

- **Hypothalamic Sleep-Wake Circuits**
  Research on the reticular activating system has identified certain neurons around the hypothalamus that are involved in sleep and wake regulation, forming what is known as the sleep center. These nuclei release wake-related neurotransmitters such as acetylcholine (Ach), norepinephrine (NE), serotonin (5-HT), dopamine (DA), histamine (His), and orexin (Orx), as well as sleep-related neurotransmitters like GABA. The involved nuclei include the basal forebrain, locus coeruleus (LC), raphe nuclei, tuberomammillary nucleus (TMN), and ventrolateral preoptic area (VLPO) of the hypothalamus [33].
- **Cortical Fragmentation Circuits**
  Under general anesthesia, cortical electrical activity fragments in both time and space. Long-distance cortical information transmission (over 2 cm) is interrupted, while short-distance cortical electrical activity (less than 4 mm) remains synchronous. This results in significant phase differences in slow-wave oscillations across distant cortical areas, with local neuronal discharge activity occurring in phase with slow waves. However, this synchronization is disrupted in

more distant cortical regions. This implies that under anesthesia, the cortex is segmented into isolated "islands," where excitation in one cortical area coincides with inhibition in distant areas, leading to a loss of information exchange and processing capabilities between cortical regions [33].

2.3.2 Pain Matrix

Traditionally, pain signals were thought to travel from the spinal cord to the brain cortex via the spinothalamic pathway. The brainstem regions possess descending inhibitory or modulatory systems that directly act on the spinal dorsal horn to modulate pain. However, recent findings reveal that more brain regions are involved in pain modulation, regulating not only the sensory component of pain but also the emotional and cognitive aspects associated with pain. Some scientists refer to the combination of brain areas closely related to pain modulation as the "pain matrix" or "Pain Matrix." This includes parts of the cingulate cortex, amygdala, primary and secondary somatosensory cortices (S1 and S2), insular cortex (IC), thalamus, periaqueductal gray (PAG) of the midbrain, prefrontal cortex (PFC), and cerebellum. These regions play significant roles in the ascending pain pathways. The Pain Matrix concept does not rigidly refer to pain modulation components but rather to brain regions related to cognitive, emotional, motivational, sensory, and pain-related neuropsychiatric functions. These functional areas collectively contribute to pain modulation, completing the perception of pain [34, 35].

2.3.3 Reward Circuits

Research indicates that stimulating specific brain regions can induce self-satisfaction and pleasure in animals. Drugs such as morphine, heroin, cocaine, amphetamines, and cannabis can continuously activate these brain regions, producing euphoria, leading to addiction and abuse. These brain regions are known as the reward system or approach system. It is understood that dopaminergic circuits from the ventral tegmental area (VTA) to the nucleus accumbens are involved. Using dopamine D3 receptor agonists in animals increases the frequency of self-stimulation, while administering D3 receptor antagonists reduces self-stimulation frequency, indicating that D3 receptors are primarily located in the nucleus accumbens [36]. If electrodes are placed in the lateral hypothalamus, dorsal midbrain, or entorhinal cortex of rats, incidental self-stimulation can cause withdrawal and avoidance behaviors, and the animals will not engage in self-stimulation again, indicating that stimulating these brain regions causes aversion and pain. These regions are referred to as the punishment system or avoidance system. Statistics show that the reward system occupies about 35% of the rat brain, the punishment system about 5%, and non-reward/non-punishment areas about 60%. Similar self-stimulation experiments in patients with schizophrenia, epilepsy, or tumors accompanied by intractable pain show comparable results [36, 37].

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The Role of Glial Cells in Anesthesia and Pain Management

3

The term "neuroglia," first introduced by Virchow in 1846, describes the substance that connects nerve cells, akin to the connective tissue found in other organs. The term "glia" is derived from the Greek word for glue, indicating a "glue-like substance" within neural tissue. Neuroglia are critical components of neural tissue, contributing significantly to its function. Remarkably, neuroglia constitute roughly half of the brain's volume and vastly outnumber nerve cells by a factor of ten. From a developmental perspective, glial cells are categorized into two main types: macroglia (originating from the neuroectoderm, including astrocytes and oligodendrocytes) and microglia (smaller cells thought to be a type of mononuclear phagocyte derived from the mesoderm). The diverse morphology of glial cells, smaller in size compared to neurons, remained largely indistinguishable for a long time due to technological limitations. However, advancements in techniques such as immunohistochemistry, cell culture, electron microscopy, and laser confocal microscopy have recently propelled the study of neuroglia's morphology and function (Fig. 3.1) [1, 2].

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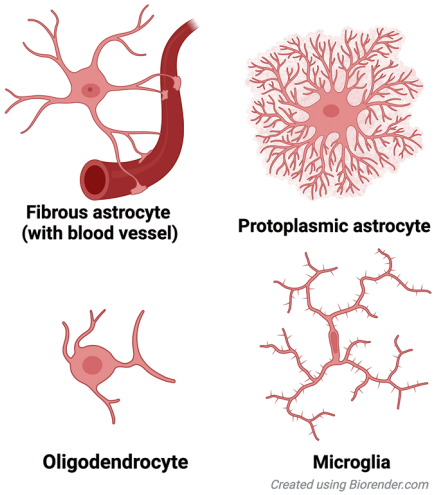

Fig. 3.1 Morphological patterns of different types of glial cells

3.1 Astrocytes

Astrocytes, named by Golgi and Cajal in the late nineteenth century through the metal impregnation method for classifying glial cells, are the most numerous among various glial cells. They constitute approximately 5% of all glial cells in the visual cortex and 30–40% in the thalamus, being widely distributed across the gray and white matter of central nervous system (CNS), as well as in the neurohypophysis (pituicytes), retina (Müller cells), ependyma (ependymal cells), and choroid plexus (choroidal cells). Traditionally, astrocytes have been attributed with several key functions [2, 3]:

- Providing structural support to neuronal cell bodies and processes through their extensive distribution.
- Retaining the ability to divide postnatally, forming glial scars in response to injury.
- Participating in material transport and the formation of the blood-brain barrier by attaching to capillaries with their end-feet.
- Playing a significant role in the metabolism of excitatory neurotransmitter glutamate (Glu) and inhibitory neurotransmitter GABA, mediating their interconversion.
- Maintaining ionic balance in the brain and synthesizing neuroactive substances.
- Surrounding synaptic structures to prevent neurotransmitter diffusion into the synaptic cleft and regulating their release.

In recent years, our understanding of astrocytes' morphological characteristics and functional activities has deepened. Below is an in-depth discussion of astrocytes' roles in pain and other neurological diseases.

3.1.1 Astrocytes and Pain

Historically, glial cells in the CNS were thought to serve merely supportive, insulating, and nutritional roles, without involvement in intercellular signal transmission. Pain signals were believed to induce excitatory changes in spinal neurons, implying that pain modulation and integration at the spinal level were solely related to spinal neurons and their neurotransmitters. However, as research progressed, it became evident that certain neuropathic pain phenomena, such as mirror-image pain (MIP) and extraterritorial pain (ETP), could not be entirely explained by this "neuron model" [4].

Research into astrocytes' role in pain began in the 1990s. It was reported that spinal astrocyte activation coincided with neuropathic pain in animal models, and inhibiting astrocyte activation alleviated neuropathic pain. Subsequent studies found astrocyte activation evidence in various neuropathic pain models. Inhibiting astrocyte activation and reducing inflammatory cytokine release have been shown to alleviate neuropathic pain. Several molecular substances of astrocytes, such as mitogen-activated protein kinases (MAPKs), chemokines (CCL2, CXCL1, CXCL10), and connexins (Cx43), are involved in pathological pain development [5].

3.1.2 Astrocytes and Epilepsy

Astrocyte proliferation leading to glial scar formation is a morphological characteristic of epilepsy. This proliferation can disrupt extracellular Na^+/K^+ balance, lowering the excitability threshold of nerve cells and resulting in seizures. Selective blockade of GABA uptake by astrocytes using the drug THPO (testosterone) can prevent sound-induced seizures in mice without affecting GABA uptake by neurons [6, 7].

3.1.3 Astrocytes and Parkinson's Disease

Parkinson's disease is characterized by motor disturbances such as tremor and rigidity. Intravenous injection of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) produces the toxic substance MPP (1-methyl-4-phenylpyridinium), which can kill dopamine cell groups, leading to parkinsonian symptoms. The conversion of MPTP to MPP involves monoamine oxidase B, which is abundant in astrocytes [8, 9].

3.1.4 Astrocytes and Huntington's Disease

Huntington's disease, characterized by hyperkinesia or chorea, is believed to result from the destruction and death of striatal neurons caused by quinolinic acid. The enzyme 3-hydroxyanthranilic acid oxygenase (3HAO), responsible for synthesizing

quinolinic acid, is predominantly found in astrocytes. Metabolic disturbances in astrocytes can lead to increased enzyme activity, resulting in excessive quinolinic acid production, striatal neuron death, and Huntington's disease onset [10].

3.1.5 Astrocytes and Immune Response

The brain, lacking a lymphatic system and having a blood-brain barrier (involving astrocytes), was once considered an "immune-privileged organ," isolated from the immune system. However, Swiss scholar Fontana challenged this view by showing that antibodies could enter the brain via cerebrospinal fluid. Certain brain regions, such as around the ventricles, lack a blood-brain barrier. Under certain conditions, activated lymphocytes can cross the blood-brain barrier into brain tissue for immune surveillance [11]. Astrocytes can mediate immune responses in the brain by functioning as antigen-presenting cells, presenting foreign antigens to the major histocompatibility complex (MHC), and stimulating T lymphocytes to initiate an immune response. Normally, the brain lacks MHC, but under certain conditions (e.g., cell culture or interferon treatment), neurons and glial cells can synthesize MHC (including classes I and II). Astrocyte-produced MHC class II antigens are associated with diseases like multiple sclerosis [12, 13].

3.2 Oligodendrocytes

Oligodendrocytes are relatively small cells within the CNS, typically found among myelinated fibers. They are closely associated with neuron somas or dendrites, acting as satellite cells, or positioned around blood vessels as perivascular cells. The cell body of an oligodendrocyte is spherical or polygonal, featuring a nucleus that stains more densely than that of astrocytes. The cytoplasm is sparse and moderately dense, containing numerous mitochondria, microtubules, free ribosomes, and a well-developed Golgi complex, with minimal glycogen. Electron microscopy reveals a nucleus with abundant heterochromatin [14, 15].

Oligodendrocytes are characterized by the expression of galactocerebroside, carbonic anhydrase II (CAII), myelin basic protein (MBP), 2′,3′-cyclic-nucleotide 3′-phosphodiesterase (CNPase), and transferrin. Antibodies targeting these molecules, along with RIP antibodies, have confirmed that oligodendrocytes are responsible for forming myelin sheaths in the CNS [16]. Each internodal segment of a myelinated fiber is created by an oligodendrocyte process that wraps around the axon in a spiral, forming concentric lamellae. A single oligodendrocyte can form 40–50 internodal segments. The term "oligodendrocyte units" refers to all axons myelinated by a single oligodendrocyte. Oligodendrocytes are classified according to the number of axons they myelinate: type I units myelinate many axons, type IV units myelinate only one, and types II and III are intermediate. Type IV units are associated with thicker axons, while types I–III are linked to thinner ones. It is proposed that all oligodendrocyte units produce a consistent amount of myelin,

resulting in thicker fibers forming thicker myelin sheaths with more lamellae and longer internodal segments. Research suggests that myelinated axons within a unit have similar diameters. Dye injections into optic nerve oligodendrocytes indicate that all internodal segments within a unit have consistent lengths. These findings suggest uniformity in the number and thickness of axons within each oligodendrocyte unit, with the number of myelin lamellae positively correlated with axon diameter [17, 18].

3.3 Microglia

Microglia, first distinguished from other neural cells in 1919 by del Rio-Hortega using the silver carbonate staining method, are small, branched cells within the CNS. Substantial evidence supports their mesodermal origin. During late embryonic development, embryonic monocytes and/or their precursors infiltrate the brain in an amoeboid form through blood vessel walls, later losing motility and transforming into typical branched microglia. In adulthood, new microglia may originate from endogenous proliferation, as mature monocytes entering the brain postnatally transform into macrophages rather than microglia [19]. Sievers et al. (1994) demonstrated that hematopoietic cells can be transformed into microglia in the brain, induced by astrocytes [20]. When monocytes are cultured on an astrocyte monolayer, they transform into dendritic cells with morphology, antigen phenotype, and unique inwardly rectifying K^+ channels similar to microglia. In rodents and possibly humans, 10–20% of glial cells are microglia, with a higher distribution in gray matter than in white matter. Under a light microscope, microglia are smaller than astrocytes and oligodendrocytes, with a long or polygonal cell body, spiny branches, and no vascular feet. The nucleus is flat or oval and stains deeply with basic dyes. Electron microscopy reveals scant cytoplasm, no glial filaments, long rough endoplasmic reticulum, and a prominent Golgi complex [21].

Microglia are primarily known for their role in immune responses within the CNS. Positioned strategically, glial cells, particularly astrocytes and microglia, serve as both producers and targets for a diverse array of cytokines, surpassing the capabilities of neurons in this regard. Upon activation, glial cells secrete cytokines that regulate their growth and functionality. For instance, patients with temporal lobe epilepsy exhibit a threefold increase in IL-1-immunoreactive microglia compared to controls. Activated microglia express higher levels of ED1, Ox-42, leukocyte common antigen, and MHC class I and II antigens and produce proteases, cytokines, and reactive oxygen and nitrogen species. The presence of MHC class II antigen-staining antibodies underscores their function as antigen-presenting cells [22, 23]. Moreover, microglia interact closely with the endocrine system, where hormones influence their uptake capacity and metabolic activities. When exposed to PMA, cultured microglia generate superoxide anions; however, this production is inhibited by the β-adrenergic agonist isoproterenol or the synthetic glucocorticoid dexamethasone, indicating that the neurotoxic effects of microglia can be mitigated through endocrine hormone actions [22].

The involvement of microglia in pain mechanisms is increasingly recognized. Significant activation changes are observed in various neuropathic pain models, including those caused by spinal or sciatic nerve compression, ligation, transection, and chemotherapeutic injuries. Activated microglia in the spinal dorsal horn display morphological changes, such as enlarged cell bodies and shortened processes, following peripheral nerve injury, with their numbers significantly increasing within 2–3 days. Noxious stimuli enhance microglial receptor expression, leading to widespread activation. These activated microglia release cytokines and excitatory substances, directly or indirectly activating pain transmission neurons and inducing central sensitization. Inhibiting microglial activation and their secreted substances can significantly reduce neuropathic pain symptoms [24].

Peripheral nerve injuries alter the phenotype and function of spinal microglia. These activated microglia establish communication pathways between neurons and glial cells and among glial cells themselves. Chemokines, purinergic receptors, and mitogen-activated protein kinases (MAPKs) play critical roles in this activation process. Elevated extracellular ATP binds to purinergic receptors, activating p38 MAPK in microglia and increasing soluble chemokine fractalkine release. Fractalkine binds to the CX3CR1 receptor on microglia, further activating p38 MAPK and releasing inflammatory mediators, creating a positive feedback loop that sustains microglial activation and promotes neuropathic pain development [25].

Activated microglia secrete substantial amounts of neuroactive substances (such as prostaglandins, neurotrophic factors, NO, and ATP) and pro-inflammatory cytokines (including IL-1, IL-6, and TNF-α), which enhance nociceptive neurotransmitter release from presynaptic primary afferents and increase postsynaptic pain-transmitting neuron sensitivity and responsiveness. This process can further activate glial cells to release additional cytokines, creating a positive feedback loop that perpetuates neuropathic pain [26, 27].

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Neurotransmitters and Receptors in Anesthesia and Pain Modulation

4

Neurotransmitters and their receptors form the foundational communication network of the nervous system, orchestrating complex processes that range from basic motor control to higher-order cognitive functions. These chemical messengers act as the language of the brain, mediating signal transmission across synapses and influencing a wide array of physiological and psychological states. Understanding the intricacies of neurotransmitter systems is essential for unraveling the mechanisms of anesthesia, pain modulation, and numerous neurological and psychiatric conditions.

The nervous system relies on a diverse repertoire of neurotransmitters, each with distinct roles, mechanisms, and target receptors. Classical neurotransmitters, such as acetylcholine and monoamines, have well-established roles in synaptic transmission and neuromodulation. Excitatory and inhibitory amino acids, like glutamate and GABA, underpin fundamental processes such as synaptic plasticity, learning, and memory. Meanwhile, neuropeptides, purines, and gaseous molecules add layers of complexity to the neurotransmitter network, modulating cellular responses and facilitating cross-system communication. Recent discoveries of endocannabinoids, neuroactive steroids, and novel gaseous transmitters such as hydrogen sulfide have further expanded our understanding of neurotransmitter diversity, underscoring their influence on both central and peripheral systems.

Receptors, the molecular gatekeepers of neurotransmitter action, are equally vital in shaping neural responses. With diverse subtypes and sophisticated regulatory mechanisms, receptors mediate the specificity and versatility of neurotransmitter effects. The dual roles of ionotropic and metabotropic receptors exemplify this complexity, enabling both rapid signal transmission and slower, modulatory effects. Advances in molecular biology and imaging have revealed the dynamic nature of receptor function, including clustering, trafficking, and regulation, which are critical for maintaining synaptic efficacy and neural plasticity. Dysregulation of these processes is implicated in numerous neurological disorders, highlighting the therapeutic potential of targeting neurotransmitter-receptor systems.

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This chapter explores the multifaceted roles of neurotransmitters and receptors in the central nervous system, with a focus on their relevance to anesthesia and pain modulation. From the classical pathways of GABAergic and glutamatergic signaling to the emerging roles of neuromodulators and retrograde messengers, the discussion provides an integrative perspective on how these systems influence sensory transmission, motor control, and consciousness. By delving into the molecular mechanisms and clinical implications of neurotransmitter-receptor interactions, this chapter aims to bridge fundamental neuroscience with anesthetic practice, offering insights into the development of more effective and precise therapeutic interventions.

4.1 Neurotransmitters

Neurotransmitters are specialized chemical substances produced by presynaptic neurons and released at their terminals. These chemicals specifically interact with receptors on postsynaptic neurons or other effector cells, leading to various physiological effects. Mammalian neurotransmitters are diverse, with over 100 types identified, and they can be categorized into several major classes based on their chemical structures [1].

4.1.1 Criteria for Identifying Neurotransmitters

A chemical is classified as a neurotransmitter if it fulfills the following criteria:

- The presynaptic neuron must possess the necessary precursors and enzyme systems to produce the neurotransmitter.
- The neurotransmitter is stored in synaptic vesicles and is released into the synaptic cleft upon stimulation by an excitatory impulse.
- Once released, the neurotransmitter binds to specific receptors on the postsynaptic membrane, inducing a physiological response. When applied artificially, it should produce the same effect in the postsynaptic neuron or effector cell.
- Mechanisms must exist to inactivate the neurotransmitter, such as enzymatic degradation or reuptake.
- Specific agonists and antagonists should be able to either mimic or inhibit the neurotransmitter's effects, respectively.

Some substances, such as nitric oxide (NO) and carbon monoxide (CO), do not fully meet these traditional criteria but still function as neurotransmitters due to their similar effects [1, 2].

4.1.2 Concept of Neuromodulators

Beyond neurotransmitters, neurons also release other chemical substances that modulate the efficacy of neurotransmitter signaling without directly transmitting information between neurons. These are known as neuromodulators. Their action is termed modulation. Neurotransmitters can act as neuromodulators and vice versa, blurring the line between the two categories.

4.1.3 Coexistence of Neurotransmitters

Historically, it was believed that a neuron would release only one type of neurotransmitter at all its terminals, a concept known as Dale's principle. This view has evolved, recognizing that neurons can contain and release multiple neurotransmitters or neuromodulators simultaneously—a phenomenon known as neurotransmitter coexistence. This allows for more nuanced physiological regulation. For instance, salivary glands receive dual innervation from parasympathetic and sympathetic nerves. Parasympathetic nerves release both acetylcholine (ACh) and vasoactive intestinal peptide (VIP); ACh stimulates saliva production, while VIP dilates blood vessels, increasing blood flow to the glands and enhancing cholinergic receptor sensitivity, leading to a large volume of watery saliva. Conversely, sympathetic nerves release norepinephrine (NE) and neuropeptide Y (NPY); NE promotes saliva secretion but reduces blood flow, while NPY constricts blood vessels, resulting in a smaller volume of thicker saliva [3].

4.1.4 Metabolism of Neurotransmitters

The metabolism of neurotransmitters involves several steps: synthesis, storage, release, degradation, reuptake, and resynthesis. ACh and amine neurotransmitters are synthesized in the cytoplasm by specific enzymes and then stored in synaptic vesicles. Peptide neurotransmitters are synthesized through ribosomal translation, regulated by genetic instructions, followed by posttranslational modifications. Neurotransmitter release from presynaptic terminals has been described previously. After their release and receptor activation, neurotransmitters are swiftly removed from the synaptic cleft through enzymatic degradation or reuptake by the presynaptic terminal. For example, ACh is broken down by cholinesterase into choline and acetate; choline is then reabsorbed by the terminal for the synthesis of new ACh. Norepinephrine (NE) is mainly removed via reuptake by the terminal, with lesser involvement of enzymatic inactivation [4].

4.1.5 Function of Neurotransmitters

Neurotransmitters and neuromodulators are crucial for a wide range of nervous system functions, influencing processes from muscle contraction to mood regulation. Their balance and interactions are essential for maintaining normal physiological functions and overall health.

Recent research has expanded our understanding of various lesser-known neurotransmitters and neuromodulators in both health and disease. For instance, endocannabinoids, which interact with cannabinoid receptors, play significant roles in regulating pain, appetite, and memory. Similarly, purinergic signaling, which involves ATP and other purines, is vital in inflammation and cell death processes.

Research into the gut-brain axis has also highlighted the significant impact of gut-produced neurotransmitters, such as serotonin, on brain function and behavior, revealing the complex interactions between different body systems [5].

In summary, understanding neurotransmitters and neuromodulators is critical for grasping the intricate workings of the nervous system and advancing our knowledge of both physiological and pathological conditions.

4.2 Receptors

Receptors are specialized biological macromolecules capable of binding neurotransmitters, drugs, or intracellular signaling molecules, leading to alterations in cellular function. In the nervous system, receptors are predominantly membrane bound and interact with neurotransmitters as their primary ligands [6]. Many clinically used drugs function as either agonists or antagonists of these receptors. Agonists bind to receptors and mimic the effects of natural ligands, whereas antagonists block the effects of natural ligands or agonists without inducing a response themselves [7]. Despite their shared characteristics, nervous system receptors have several distinctive features.

4.2.1 Receptor Subtypes

Receptors are categorized into multiple subtypes. For instance, cholinergic receptors are divided into muscarinic (M) and nicotinic (N) types. Nicotinic receptors are further classified into N1 and N2 subtypes. Adrenergic receptors are divided into alpha (α) and beta (β) types, with α receptors further split into α1 and α2 subtypes and β receptors into β1, β2, and β3 subtypes. This subdivision allows a single neurotransmitter to exert a wide range of biological effects by interacting with different receptor subtypes [8].

4.2.2 Presynaptic Receptors

While receptors are typically located on the postsynaptic membrane, they can also be present on the presynaptic membrane. Presynaptic receptors modulate neurotransmitter release from the presynaptic terminal, influencing whether neurotransmitter release is enhanced or inhibited. For instance, norepinephrine (NE) acting on presynaptic receptors can inhibit further NE release. These receptors are known as autoreceptors. Conversely, some presynaptic receptors, such as the angiotensin receptor on sympathetic nerve terminals, facilitate neurotransmitter release when activated by angiotensin I [9].

4.2.3 Mechanism of Receptor Action

Receptors initiate cellular effects through specific transmembrane signaling pathways once they bind with neurotransmitters. The primary types of receptors involved in these pathways are G-protein-coupled receptors (GPCRs) and ion channel receptors. GPCRs, which are more prevalent, mediate various intracellular signaling cascades, while ionotropic receptors directly influence ion flow across membranes [10].

4.2.4 Receptor Clustering

Receptors often cluster on the postsynaptic membrane in response to presynaptic activity. This clustering is facilitated by binding proteins specific to the receptors. For example, at the neuromuscular junction, rapsyn binds to nicotinic receptors. For glutamate and GABAA receptors, clustering is linked with PR2-binding proteins and gephyrin proteins, respectively [11]. During neuronal activity, receptors can move toward and bind with gephyrin, leading to their aggregation on the postsynaptic membrane. In contrast, during periods of inactivity, receptors may disperse [12].

4.2.5 Receptor Regulation

The number and affinity of membrane receptors for neurotransmitters can vary under different physiological and pathological conditions. When neurotransmitter release is low, receptor numbers and affinity typically increase, a process known as receptor upregulation. Conversely, excessive neurotransmitter release can lead to receptor downregulation, reducing receptor numbers and affinity. Receptors can be mobilized from intracellular stores to the membrane or internalized into the cell, affecting functional receptor levels. Regulatory changes in receptor affinity are often mediated by phosphorylation or dephosphorylation of receptor proteins. These processes ensure that receptor function is finely tuned according to cellular needs [13].

Recent advancements have also highlighted the role of receptor dynamics in disease states. Abnormalities in receptor expression and function are associated with various neurological and psychiatric disorders, emphasizing the importance of understanding receptor mechanisms in therapeutic development [14].

4.3 Major Neurotransmitters and Receptor Systems in the Central Nervous System

4.3.1 Acetylcholine and Its Receptors

Recent research underscores the integral role of acetylcholine (ACh) and its receptors in maintaining cognitive functions and modulating behavioral responses. Understanding these systems is essential for developing treatments for disorders related to cholinergic dysfunction, such as Alzheimer's disease and other cognitive impairments [6].

- ACh is a neurotransmitter derived from choline and acetate. Neurons that utilize ACh are termed cholinergic neurons. These neurons are extensively distributed throughout the central nervous system (CNS), including the motor neurons located in the anterior horn of the spinal cord, specific sensory projection neurons in the ventral posterior nucleus of the thalamus, and various components of the brainstem reticular activating system, striatum, basal forebrain nuclei, limbic system, amygdala, and hippocampus. Neurons that release ACh are known as cholinergic fibers.
  Cholinergic receptors are specialized proteins that bind with ACh. They are categorized into two main types based on their pharmacological responses: muscarinic receptors (M receptors) and nicotinic receptors (N receptors). These receptors are named after their interaction with the plant alkaloids muscarine and nicotine, respectively, which produce muscarinic and nicotinic effects. Both types of cholinergic receptors are found throughout the CNS. Neurons that respond to ACh are referred to as cholinergic-responsive neurons. The central cholinergic system plays a crucial role in a wide range of CNS functions, including cognitive processes like learning and memory, states of arousal and sleep, sensory and motor activities, autonomic functions, and emotional regulation [15].

4.3.2 Monoamine Neurotransmitters and Their Receptors

Monoamine neurotransmittersencompass norepinephrine (NE), dopamine (DA), serotonin (5-hydroxytryptamine, 5-HT), and histamine. Among these, norepinephrine and dopamine are categorized as catecholamines due to their shared catechol structure [6].

- **Norepinephrine and Its Receptors**
  Norepinephrine (NE) acts as a neurotransmitter in both the CNS and peripheral nervous system. Neurons that release NE are referred to as noradrenergic neurons. In the CNS, the principal cell bodies of these neurons are situated in the lower brainstem, including the reticular formation of the midbrain, the locus coeruleus in the pons, and the ventrolateral medullary reticular formation. NE fibers project to various brain regions, such as the cerebral cortex, limbic forebrain, and hypothalamus, as well as to the spinal cord's dorsal, lateral, and anterior horns [7].
  Adrenergic receptors, which interact with NE, are dispersed throughout the CNS. These receptors are classified into alpha (α) and beta (β) types, with α receptors further divided into α1 and α2 subtypes. α2 receptors are predominantly located presynaptically and influence neurotransmitter release, while β receptors are categorized into β1, β2, and β3 subtypes. All adrenergic receptors are G-protein-coupled receptors. NE and its receptors play critical roles in managing cardiovascular function, mood, thermoregulation, appetite, and alertness. Clinically, α2 receptor agonists like clonidine are utilized to manage hypertension by diminishing central NE release. Additionally, the discovery of imidazoline receptors with hypotensive effects and structural similarities to α2 receptors highlights potential common regulatory mechanisms [7].
- **Dopamine and Its Receptors**
  Dopamine is primarily found within the CNS and is involved in pathways such as the nigrostriatal, mesolimbic, and tuberoinfundibular systems. The nigrostriatal pathway regulates motor control, the mesolimbic pathway is associated with reward and addiction, and the tuberoinfundibular pathway manages pituitary hormone secretion. Age-related declines in dopamine receptor density, especially in males, have been observed using PET imaging.
  There are five known dopamine receptors (D1 through D5), all of which are G protein coupled. The dopamine system governs motor functions, emotional states, pituitary activities, and cardiovascular functions [7].
- **Serotonin and Its Receptors**
  Serotonin (5-HT) is predominantly found in platelets, enterochromaffin-like cells of the gastrointestinal tract, and the intermuscular nerve plexus. Within the CNS, 5-HT neurons are concentrated in the raphe nuclei of the lower brainstem, projecting to the hypothalamus, limbic system, neocortex, cerebellum, and spinal cord.
  At least seven distinct 5-HT receptors (5-HT1 to 5-HT7) exist, with various subtypes for each. Most 5-HT receptors are G protein coupled, except for the ionotropic 5-HT3 receptor. The serotonin system is complex, influencing pain perception, mood regulation, sleep patterns, body temperature, sexual behavior, and pituitary functions [7].
- **Histamine and Its Receptors**
  Histaminergic neurons are located in the posterior hypothalamus, particularly within the tuberomammillary nucleus, and extend their projections throughout

the CNS, including the cerebral cortex and spinal cord. Histamine is also present in mast cells and enterochromaffin-like cells of the gastric mucosa.

Three histamine receptors are recognized (H1, H2, and H3), each found in both the CNS and peripheral nervous system. H3 receptors, predominantly presynaptic, modulate the release of histamine and other neurotransmitters through G-protein-coupled mechanisms. Histamine's interaction with H1 receptors activates phospholipase C, while H2 receptors elevate intracellular cAMP levels. The central histamine system is involved in regulating alertness, sexual behavior, pituitary hormone secretion, blood pressure, thirst, and nociception [7].

4.3.3 Amino Acid Neurotransmitters and Their Receptors

- **Excitatory Amino Acid Neurotransmitters and Their Receptors**
  Excitatory amino acid neurotransmitters primarily include glutamate (Glu) and aspartate (Asp). Glu serves as the chief excitatory neurotransmitter within the brain and spinal cord, being particularly prevalent in the cerebral cortex and the dorsal horn of the spinal cord. Aspartate is predominantly located in the pyramidal and stellate cells of the visual cortex.

  Glu receptors are extensively distributed throughout the CNS and are categorized into ionotropic (iGluRs) and metabotropic (mGluRs) types. Ionotropic receptors comprise kainate (KA) receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, and N-methyl-D-aspartate (NMDA) receptors, each with multiple subtypes. These receptors differ in their kinetics, ion conductance, and permeability. For instance, NMDA receptors require glycine binding for activation, are blocked by Mg^{2+} under resting conditions, and can be modulated by compounds such as PCP and ketamine. Metabotropic glutamate receptors (mGluRs) are classified into 11 subtypes and are integral to processes like synaptic plasticity, motor coordination, and spatial learning [1, 16].
- **Inhibitory Amino Acid Neurotransmitters and Their Receptors**
  Gamma-aminobutyric acid (GABA) and glycine (Gly) are the primary inhibitory neurotransmitters. GABA is the main inhibitory neurotransmitter in the brain, particularly abundant in the superficial layers of the cerebral cortex and the Purkinje cell layer of the cerebellum. Glycine is predominantly found in the spinal cord and brainstem.

  GABA receptors are classified into GABAA, GABAB, and GABAC types. GABAA and GABAC receptors are ionotropic chloride channels, whereas GABAB receptors are metabotropic and modulate potassium (K^+) and chloride (Cl^-) currents through G-protein-coupled pathways. Glycine receptors share similarities with GABAA receptors, functioning as ionotropic chloride channels that generate inhibitory postsynaptic potentials (IPSPs) upon activation [1, 16].

4.3.4 Neuropeptides and Their Receptors

Neuropeptides are small peptide molecules in the nervous system that either transmit or modulate neural signals. Major categories include:

- **Tachykinins**
  Mammalian tachykinins include substance P, neurokinin A, neuropeptide K, neuropeptide α, neurokinin A, and neurokinin B. Tachykinin receptors, including NK-1, NK-2, and NK-3, are G-protein-coupled receptors that activate phospholipase C. Substance P is notably concentrated in primary afferent fibers of the spinal cord, where it may modulate pain transmission. It is also present in the nigrostriatal pathway and contributes to neuroendocrine regulation within the hypothalamus [2].
- **Opioid Peptides**
  A variety of active opioid peptides, such as endorphins, enkephalins, and dynorphins, have been identified. The main opioid receptors are μ, κ, and δ, all of which are G-protein-coupled receptors that decrease cAMP levels. These receptors are distributed throughout the brain and body, with their effects varying based on the interactions between specific ligands and receptors [2].
- **Hypothalamic and Pituitary Neuropeptides**
  Peptides produced in the hypothalamus, including somatostatin, corticotropin-releasing hormone (CRH), and thyrotropin-releasing hormone (TRH), play roles as neurotransmitters [17]. Somatostatin receptors (SSTR1-SSTR5) are involved in sensory, motor, and cognitive functions. CRH and its receptors are located in the cerebral cortex and cerebellar pathways, while TRH is concentrated in the cerebral cortex, hippocampus, spinal cord, and retina [18].
- **Brain-Gut Peptides**
  Brain-gut peptides, such as cholecystokinin (CCK), are present in both the digestive tract and the brain. CCK-8 is the predominant form in the brain, with distribution in the cerebral cortex, striatum, amygdala, hypothalamus, and midbrain. CCK receptors (CCKA and CCKB) are G protein coupled and influence feeding behaviors [19].
- **Other Peptide Neurotransmitters**
  Additional peptides within the CNS include bradykinin, angiotensin I, endothelin, atrial natriuretic peptide, calcitonin gene–related peptide, and neuropeptide Y. These peptides can either excite or inhibit neuronal activity, participating in a wide range of regulatory processes within the nervous system.

4.3.5 Purine Neurotransmitters and Their Receptors

Purine neurotransmitters, such as adenosine and ATP, play significant roles in the CNS. Adenosine predominantly exerts inhibitory effects, though it can also have excitatory influences depending on the receptor subtype it binds to. The adenosine receptors, classified into A1, A2A, A2B, and A3, are all G protein coupled [20].

Activation of A1 and A3 receptors typically results in a decrease in cyclic AMP (cAMP) levels, whereas stimulation of A2A and A2B receptors leads to an increase in cAMP levels. The inhibitory effects of adenosine are mainly mediated through A1 receptors, while excitatory actions are primarily associated with A2 receptors [21].

4.3.6 Gaseous Neurotransmitters

- **Nitric Oxide (NO)**
  Nitric oxide (NO) is synthesized from L-arginine by the enzyme nitric oxide synthase (NOS). Unlike traditional neurotransmitters, NO is not stored in vesicles nor released via exocytosis. Instead, it diffuses freely to nearby target cells, where it binds to and activates soluble guanylate cyclase, subsequently increasing intracellular levels of cyclic GMP (cGMP). NOS is widely distributed across the brain, with notable concentrations in regions such as the cerebellum, colliculi, olfactory bulb, cerebral cortex, hippocampus, and septum. NO plays crucial roles in synaptic plasticity, including mechanisms like long-term potentiation (LTP) and long-term depression (LTD) [22]. However, excessive NO production can be neurotoxic, leading to cell death [23].
- **Carbon Monoxide (CO)**
  Carbon monoxide (CO) is generated during the breakdown of heme by the enzyme heme oxygenase (HO). There are two isozymes of HO: HO-1, found in glial cells and some neurons, and HO-2, which is highly concentrated in neurons within the cerebellum and hippocampus. Similar to NO, CO activates guanylate cyclase, leading to increased cGMP levels, which mediates its biological effects [24, 25].
- **Hydrogen Sulfide (H_2S)**
  Hydrogen sulfide (H_2S) has recently been recognized as a gaseous neurotransmitter. It is produced endogenously by enzymes such as cystathionine beta-synthase (CBS) and cystathionine gamma-lyase (CSE). H_2S can modulate neuronal signaling by interacting with various ion channels and enzymes. It has been implicated in neuroprotection, synaptic plasticity, and the regulation of oxidative stress [26]. The physiological and pathophysiological roles of H_2S in the nervous system are areas of active research [27].

4.3.7 Other Potential Neurotransmitters

- **Endocannabinoids**
  Endocannabinoids, such as anandamide and 2-arachidonoylglycerol (2-AG), are lipid-based neurotransmitters that bind to cannabinoid receptors (CB1 and CB2) in the brain. These neurotransmitters are involved in regulating mood, appetite,

pain sensation, and memory [28]. Endocannabinoids are synthesized on demand and act as retrograde messengers, modulating the release of other neurotransmitters [29].

- **Prostaglandin**
  There is evidence suggesting that neuronal membranes contain a prostaglandin transporter, indicating that prostaglandins may influence neuronal activity by modulating cAMP levels rather than functioning as conventional neurotransmitters [30].
- **Neuroactive Steroids**
  Additionally, various steroid hormones, referred to as neuroactive steroids, have significant impacts on brain function. These steroid hormones can easily cross into the CNS from the bloodstream, and many neurons possess receptors for sex hormones and adrenal corticosteroids. Neuroactive steroids can exert rapid effects, likely mediated by membrane receptors, in addition to their actions on nuclear receptors [31]. Furthermore, some simpler steroid precursors can be converted into biologically active neuroactive steroids within the brain. For instance, progesterone is known to promote myelin formation [32]. However, the broader regulatory roles of steroids in brain function are still under extensive investigation.

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5 Intracranial Pressure, Cerebral Blood Flow, and Brain Metabolism: Implications for Anesthesia and Critical Care

The intricate interplay between intracranial pressure (ICP), cerebral blood flow (CBF), and brain metabolism is fundamental to maintaining normal brain function and represents a critical focus in both neuroscience and clinical anesthesiology. These physiological parameters are tightly regulated through complex mechanisms to ensure adequate oxygen and nutrient delivery while protecting the brain from ischemic injury and metabolic disturbances. Understanding these processes is particularly crucial in neuroanesthesia, where interventions directly impact cerebral hemodynamics and metabolism.

ICP, a key determinant of cerebral perfusion, is influenced by multiple factors, including body position, arterial gases, and systemic blood pressure. Elevated ICP can precipitate life-threatening complications such as cerebral edema, brain herniation, and Cushing's phenomenon. Meanwhile, CBF supports the brain's high metabolic demand and is governed by autoregulatory mechanisms that respond dynamically to changes in pressure, oxygen, carbon dioxide, and pH levels. Disruptions in this delicate balance can lead to catastrophic outcomes, especially during surgeries or critical care scenarios.

The brain's metabolic processes, predominantly reliant on glucose and oxygen, underscore its vulnerability to fluctuations in energy supply. With minimal energy reserves, the brain depends on continuous blood flow to sustain neurophysiological functions. Advances in imaging technologies, such as functional magnetic resonance imaging (fMRI) and blood oxygen level-dependent (BOLD) imaging, have illuminated the relationship between CBF and neural activity, providing valuable insights into cerebral metabolism and its alterations under anesthesia.

This chapter explores the fundamental principles governing ICP, CBF, and brain metabolism, emphasizing their interdependence and relevance to anesthesia practice. By examining physiological mechanisms, clinical implications, and recent research, it aims to provide a comprehensive understanding of how these factors influence anesthetic management and patient outcomes in neurocritical and surgical settings. This knowledge not only enhances the precision of anesthesia care but also

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offers avenues for neuroprotection and improved recovery in patients with brain injuries or undergoing complex neurosurgical procedures.

5.1 Intracranial Pressure

Intracranial pressure (ICP) refers to the pressure within the cranial cavity, which is confined by the rigid skull and contains brain tissue, blood, and cerebrospinal fluid (CSF). The standard method for measuring ICP involves a lumbar puncture performed while the patient is lying on their side, and the pressure is gauged using a specific pressure tube with an internal diameter of 2 mm to 3 mm [1]. In adults, normal ICP ranges from 5.3 mmHg to 13.5 mmHg. Values between 13.5 mmHg and 15 mmHg suggest potential elevation in ICP, while readings above 15 mmHg confirm increased ICP. Conversely, ICP values between 3.8 mmHg and 5.3 mmHg indicate possible low ICP, with values below 3.8 mmHg confirming low ICP. Typically, the volumes of brain tissue, cerebral blood, and CSF are balanced within the cranial cavity, maintaining a stable ICP [1, 2].

5.1.1 Major Factors Influencing ICP

- **Influence of Body Position on ICP**
  Body positioning can significantly affect ICP. Elevating the head of the bed to 30 ° can help reduce ICP by promoting venous outflow. However, extreme head elevation or flexion should be avoided as it can impede venous drainage and increase ICP [3].
- **Impact of Arterial Carbon Dioxide Levels on ICP**
  The arterial carbon dioxide tension ($PaCO_2$) significantly influences ICP through its effect on cerebral blood flow (CBF). When $PaCO_2$ fluctuates dramatically between 20 mmHg and 60 mmHg, CBF changes accordingly, resulting in alterations in cerebral blood volume and ICP. Clinically, hyperventilation can reduce $PaCO_2$, thereby decreasing CBF and lowering ICP [4].
- **Impact of Arterial Oxygen Levels on ICP**
  Within the arterial oxygen tension (PaO_2) range of 60 mmHg to 135 mmHg, CBF and ICP remain relatively stable. However, when PaO_2 falls below 50 mmHg, both ICP and CBF increase. Prolonged hypoxia can lead to cerebral edema, preventing ICP normalization even after oxygen levels are corrected. Elevated oxygen levels can slightly reduce CBF and ICP, with this effect being more pronounced under hyperbaric conditions [5].
- **Impact of Blood Pressure on ICP**
  When mean arterial pressure (MAP) is between 60 mmHg and 150 mmHg, CBF is regulated through autoregulation, minimizing the impact of blood pressure on ICP. Outside this range, ICP changes linearly with blood pressure fluctuations. Increased central venous pressure can elevate cerebral venous pressure, raising ICP. Elevated thoracic and abdominal pressures, as well as actions such as

coughing, can dilate spinal veins and increase CSF pressure. During anesthesia, various factors can elevate ICP, including tracheal intubation, extubation, perioperative agitation, coughing, and changes in surgical positioning (e.g., Trendelenburg position). Therefore, multiple measures should be taken to prevent increased ICP during neurosurgical anesthesia [5].

- **Age-Related Factors in ICP Compensation**
  In infants and young children, unsealed cranial sutures allow for suture separation to alleviate increased ICP. In elderly individuals, brain atrophy provides more compensatory space, potentially prolonging disease progression. Malignant tumors cause rapid and severe increases in ICP, whereas benign tumors grow slowly, resulting in later and less severe symptoms. The location of lesions also affects the course of ICP increase. Lesions in the midline and posterior fossa can block CSF circulation, leading to early ICP increases. Lesions near large intracranial venous sinuses can impede venous return, causing early ICP increase [6].

5.1.2 Physiological Dysfunctions Caused by Elevated ICP

- **Cushing's Phenomenon**
  Through his experiments on canines, Cushing observed that infusing isotonic saline into the subarachnoid space to elevate ICP resulted in notable physiological changes. When ICP neared the diastolic pressure, the dogs developed marked hypertension, slow heart rate (bradycardia), and widened pulse pressure. Further increases in ICP led to Cheyne-Stokes respiration, hypotension, weak pulse, and ultimately respiratory and cardiac arrest, a series of events collectively known as Cushing's phenomenon [7].
- **Cerebral Edema**
  Elevated ICP can disrupt cerebral blood flow and metabolism, leading to cerebral edema, which further increases brain volume and exacerbates ICP [8]. Clinically, cerebral edema associated with brain injuries and tumors often manifests initially as vasogenic edema, while hypoxia and ischemia typically result in cytotoxic edema [9].
- **Brain Herniation**
  Excessive ICP can force adjacent or distant brain tissues into specific physiological spaces or openings, leading to a condition known as brain herniation, characterized by distinct clinical symptoms depending on the herniation site [10, 11].
- **Gastrointestinal Dysregulation**
  Some patients primarily exhibit gastrointestinal symptoms such as peptic ulcers, perforations, and bleeding, which may be linked to autonomic dysfunction caused by elevated ICP impacting the hypothalamus [12].
- **Compromised Cerebral Blood Flow Autoregulation**
  Elevated ICP impairs the brain's ability to regulate its own blood flow. Cerebral perfusion pressure (CPP), defined as mean arterial pressure (MAP) minus ICP, becomes increasingly dependent on the balance between blood pressure and ICP

as ICP rises. In severe cases, draining cerebrospinal fluid can alleviate ICP and improve cerebral blood flow [13, 14].

- **Brainstem Hemorrhage and Occipital Lobe Infarction**
  Increased ICP can lead to hemorrhages in the brainstem, particularly in the midbrain and pons, likely due to the stretching of arteries, especially the penetrating branches of the basilar artery. Herniation through the tentorium can compress the posterior cerebral artery, resulting in infarction of the occipital lobe [15].

5.2 Cerebral Blood Flow

The human brain, although constituting just 2–3% of body weight, demands a substantial blood supply of roughly 750–1000 ml/min, representing about 15–20% of the heart's output. The distribution of cerebral blood flow (CBF) is not uniform, with an average of 54 ml/100 g of brain tissue per minute [16]. Gray matter receives a higher blood flow, averaging 76 ml/(100 g·min), compared to white matter, which receives about 20 ml/(100 g·min). The cerebral cortex, within the gray matter, exhibits the highest CBF at approximately 80 ml/(100 g·min), while the central gray matter can reach 138 ml/(100 g·min) [17]. The concept of critical CBF defines thresholds for the maintenance of electrical and metabolic functions. A CBF around 16–17 ml/(100 g·min) is associated with electroencephalography (EEG) failure, while levels above 24 ml/(100 g·min) show no ischemic changes. Under halothane anesthesia, a CBF below 18 ml/(100 g·min) indicates EEG ischemia [18]. Somatosensory evoked potentials are maintained at 20 ml/(100 g·min) but decline rapidly at 12 ml/(100 g·min). Ion pump failure occurs at a CBF of around 10 ml/(100 g·min), marked by significant increases in extracellular potassium and intracellular calcium, with extracellular potassium levels exceeding 10 μmol/ml indicating pump failure. Brain edema typically forms at a threshold of 20 ml/(100 g·min), with intracellular water shifting below this value [19].

5.2.1 Autoregulation of Cerebral Blood Flow

CBF autoregulation is the brain's innate mechanism to maintain stable blood flow despite variations in cerebral perfusion pressure (CPP), ensuring consistent cerebral metabolism. This autoregulatory capability is essential for normal brain function. In healthy adults, autoregulation operates within a mean arterial pressure (MAP) range of 60 to 160 mmHg [17]. However, conditions such as stroke, hypertension, brain trauma, and tumors can impair this autoregulatory function, which may recover over time but often remains inconsistent, reducing the brain's resilience to further injury [20].

- **CPP and Autoregulation**

CPP, the difference between the mean arterial pressure entering and the mean venous pressure exiting the skull, is crucial for CBF [21]. Normally, jugular venous pressure approximates right atrial pressure, making CBF dependent on carotid artery pressure. When carotid pressure rises, CBF increases, and vice versa. Autoregulation typically overrides these effects. If arterial perfusion pressure exceeds the upper autoregulatory limit, capillary pressure rises, leading to edema from excessive fluid leakage. Below the lower limit, CBF declines linearly, causing functional impairment. The minimum perfusion pressure necessary to maintain constant CBF is the lower autoregulatory limit [22].

- **Cerebral Vascular Resistance and Autoregulation**

Normal cerebrovascular resistance ranges from 1.3 to 1.6 mmHg/(100 g·min). With constant CBF and ICP, resistance is proportional to MAP. Autoregulation maintains steady CBF by adjusting resistance; increased CPP raises resistance and vice versa. Beyond autoregulatory limits, resistance decreases, increasing CBF. In hypertension, the upper limit shifts upward, increasing resistance to protect against hyperperfusion damage. In atherosclerosis, resistance increases due to narrowed vessels, but autoregulation compensates with elevated MAP, maintaining constant CBF. Without this compensation, cerebral ischemia symptoms occur. Reduced vascular elasticity or dilation lowers resistance, increasing CBF. With constant vessel diameter and CPP, CBF inversely correlates with blood viscosity [23].

- **ICP and Autoregulation**

Acute increases in ICP from trauma trigger systemic vascular responses, including elevated blood pressure, bradycardia, irregular respiration, and hyperthermia, collectively known as Cushing's response, which protects CBF stability. CPP significantly influences CBF in the context of elevated ICP. As ICP gradually rises with CPP above 100 mmHg, CBF remains unchanged; it declines significantly when CPP drops to 51–60 mmHg. Controlled release of cerebrospinal fluid can reduce ICP and increase CBF in severe cases [22].

- **Principles of CBF Autoregulation**

CBF autoregulation is a complex process with mechanisms not fully understood. Four main theories explain it:

1. **Myogenic theory:** Proposed by Bayliss in 1902, this theory suggests that pressure-sensitive calcium channels activate with increased transmural pressure, causing smooth muscle contraction, vessel narrowing, and reduced CBF [24].
2. **Metabolic theory:** Decreased CBF triggers the release of vasodilators like CO_2, H^+, adenosine, and K^+, which increase CBF [24].

3. **Neurogenic theory:** Autonomic nerves around vessels influence CBF, but experiments show autoregulation persists even when autonomic inputs are removed, indicating a minor role of neurogenic factors [25].
4. **Endothelial theory:** Factors like nitric oxide (NO) are crucial for autoregulation. Endothelial cell integrity is vital for vascular responses; damage impairs function. Inhibiting cyclooxygenase or endothelial factors like NO disrupts autoregulation [23].

5.2.2 Chemical Control of Cerebral Blood Flow

Chemical control of CBF encompasses both internal and external elements such as oxygen, carbon dioxide, CSF pH, H^+, K^+, and adenosine [26].

- **Oxygen Regulation**

The oxygen level in arterial blood influences CBF, ensuring adequate oxygen supply for brain metabolism. This mechanism involves various factors, with adenosine playing a significant role. When partial pressure of oxygen (PaO_2) exceeds 50 mmHg, CBF is stable. Below this threshold, CBF increases and can quadruple when PaO_2 falls to 15 mmHg [27].

- **Carbon Dioxide Regulation**

The partial pressure of carbon dioxide ($PaCO_2$) in the blood greatly impacts CBF by altering the pH of the CSF. The relationship between $PaCO_2$ and CBF is linear within the range of 25 mmHg to 75 mmHg, with CBF increasing by 4% for every 1 mmHg rise in $PaCO_2$. Doubling $PaCO_2$ to 80 mmHg results in a doubling of CBF, whereas halving $PaCO_2$ to 20 mmHg results in halved CBF. Beyond 75 mmHg, the increase in CBF plateaus due to maximal vasodilation and loss of autoregulation. Clinically, hyperventilation is used to reduce $PaCO_2$ and thus decrease CBF, helping to manage intracranial pressure (ICP) [27].

- **Additional Chemical Factors**

The pH of CSF influences CBF by modifying vessel wall tension: acidic CSF causes dilation, while alkaline CSF causes constriction. Carbon dioxide crosses the blood-brain barrier easily, but bicarbonate does so slowly, making CSF pH largely dependent on CO_2 levels. Potassium concentrations in the CSF affect vascular tone, with moderate increases causing vasodilation and extreme levels leading to constriction. Adenosine, a byproduct of metabolism, dilates cerebral vessels by affecting calcium uptake in smooth muscle cells [28].

5.3 Brain Metabolism

The brain boasts an exceptionally rich blood supply; despite comprising only 2% of body weight, it receives 15–20% of the heart's output, equating to roughly 800 ml/min [29]. The internal carotid arteries deliver about two-thirds of this cerebral blood flow, with the vertebral arteries supplying the remainder. The circle of Willis plays a crucial role in mixing and distributing blood from both the internal carotid and vertebral arteries, safeguarding the brain against hypertension. In the brain's gray matter, average blood flow is between 60 and 100 ml/(100 g·min), while in the white matter, it is about 25 ml/(100 g·min), though local cerebral blood flow can vary widely [22].

The brain's metabolic rate is notably high, with 60% of its energy expenditure dedicated to neurophysiological functions and 40% to maintaining structural integrity. A significant portion of this energy is used to sustain the ion concentration gradient, which is vital for electrophysiological activities. The remaining energy supports the stabilization of the intracellular environment, encompassing membrane functions, neurotransmitter synthesis, transport, and reabsorption [30]. Glial cells, which constitute half of the brain's volume, consume substantially less energy compared to neurons. Besides providing structural support, glial cells play multiple roles: they reabsorb neurotransmitters, supply metabolic substrates, clear metabolic waste, and buffer ions [31].

Understanding brain metabolism is crucial for comprehending how the brain functions and responds to various physiological and pathological conditions. It also underscores the importance of maintaining adequate cerebral blood flow and energy supply to support the brain's demanding activities.

5.3.1 Energy Metabolism of the Brain

The brain's normal physiological functions demand a consistent and ample supply of energy. In a resting state, an adult brain's energy metabolism reaches 1.05 J/min, whereas the body's basal metabolism stands at 5.23 J/min. Although the brain represents less than 2% of the body's weight, it consumes 20% of the body's metabolic energy [30]. Typically, the brain's respiratory quotient is 1, signifying that glucose is its primary energy substrate. The brain has limited glycogen stores, and the significant disparity in glucose levels between arterial and venous blood highlights its dependence on blood glucose. The brain's glucose consumption constitutes approximately one-quarter of the body's total glucose usage. Under normal conditions, the brain can absorb 10 mg of glucose per 100 ml of cerebral blood flow. With an average cerebral blood flow of 750 ml/min at rest, the brain absorbs 75 mg of glucose each minute [32]. When cerebral blood flow diminishes, the absorption rate increases. Primarily, the glucose required by the brain originates from liver glycogen breakdown, with additional contributions from muscles and other organs. Compared to other tissues, brain tissue has exceptionally high hexokinase activity, facilitating efficient glucose utilization. Under normal circumstances, glucose in the

brain undergoes mainly aerobic metabolism, with anaerobic glycolysis accounting for only 5–15% [31]. Breaking down 10 mg of glucose requires 6.5 ml of oxygen within 8–10 seconds. Eighty-five percent of the glucose taken up by the brain converts to carbon dioxide and water, generating energy, while the remaining 15% is partially metabolized to lactate, with only a small amount stored as glycogen in brain tissue. Although glucose can be synthesized from noncarbohydrate sources (such as amino acids and fats), gluconeogenesis is not the primary energy source for the brain. The brain contains enzymes for ketone body oxidation, and under certain conditions, it can derive energy from ketone bodies. When blood circulation ceases, the brain loses its supply of oxygen and glucose, depleting stored ATP and glycogen within 10 min, leading to rapid loss of function. Clinically, cessation of cerebral blood supply for 5–10 seconds can result in syncope, followed by convulsions, and prolonged cessation (4–5 min) can be life-threatening [33].

5.3.2 Brain Metabolism and Brain Function

In normal situations, brain metabolism is intimately linked to brain function. Variations in local brain metabolism reflect changes in brain activity, ensuring the central nervous system remains stable amidst diverse internal and external environments. Research using 2-deoxy-D-[14C]glucose ([14C]DG) in rat brains has demonstrated that regions like the cortex, thalamus, geniculate bodies, and colliculi have higher glucose use compared to the pontine gray matter and cerebral white matter [34]. Under anesthesia, the metabolic rate and blood flow in almost all brain regions drop compared to the awake state. A decrease in brain activity is mirrored by a reduction in metabolic rate. In patients with primary dementia, reduced cerebral oxygen consumption correlates with the severity of the condition. During electrically induced seizures, increased brain activity is accompanied by heightened oxygen and glucose metabolism. When local brain function shifts, the corresponding areas exhibit changes in oxygen and glucose metabolism. For example, stimulating the olfactory bulb and auditory receptors boosts blood flow and metabolic rate in the relevant olfactory and auditory brain regions. Various anesthetics can lower the cerebral metabolic rate of oxygen, providing a basis for their use in brain protection during clinical procedures [35]. Additionally, hypothermia greatly reduces the metabolic rates of oxygen and glucose, and deep hypothermia techniques are frequently employed in complex cardiac and pulmonary surgeries to lower metabolic rates and safeguard brain function.

The interrelationship between local cerebral blood flow, metabolism, and brain activity forms the foundation for functional magnetic resonance imaging (fMRI) [36]. When a specific brain region's function is heightened, it is accompanied by dynamic changes in local blood flow, blood volume, oxygen uptake, and glucose metabolism. Increased levels of oxygenated hemoglobin and decreased levels of deoxygenated hemoglobin occur. Deoxygenated hemoglobin, being paramagnetic, creates local gradient magnetic fields that lead to rapid proton dephasing. By using MRI systems to capture images, the signal intensity in activated brain regions

increases, resulting in functional imaging maps. This technique is known as blood oxygen level-dependent contrast brain functional imaging (BOLD-fMRI). Functional MRI can pinpoint the location, size, and extent of brain activation areas, providing detailed anatomical positions of these areas with high temporal and spatial resolution, repeatability, and no radiation exposure [37]. Widely utilized in psychology, neuroscience, and anesthesiology research, this technology has yielded significant findings. In the near future, real-time intraoperative brain functional imaging is anticipated to monitor brain function changes during anesthesia, becoming a crucial tool for anesthesiologists and playing a pivotal role in uncovering the mysteries of anesthesia.

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The Impact of Anesthesia on Brain Bioelectrical Activity and Clinical Applications

6

The brain's bioelectrical activity plays a critical role in understanding consciousness, neural function, and the effects of anesthetic agents. Electroencephalography (EEG) and evoked potentials provide essential insights into the brain's electrical behavior, making them invaluable tools in both clinical anesthesia and neuroscience research. These modalities allow for the assessment of anesthesia depth, detection of neural pathway integrity, and monitoring of intraoperative neural function. Advances in signal processing and the integration of machine learning have further enhanced the utility of brain electrical activity monitoring, enabling real-time analysis and personalized anesthesia management. This chapter delves into the mechanisms and clinical applications of brain bioelectrical activity under anesthesia, offering a comprehensive overview of EEG patterns, anesthesia depth indices like BIS and Narcotrend, and the diagnostic significance of evoked potentials in guiding surgical safety and optimizing patient outcomes.

6.1 Spontaneous Brain Electrical Activity and Electroencephalogram (EEG)

Spontaneous brain electrical activity refers to the rhythmic potential fluctuations generated by the cerebral cortex without any apparent external stimuli. The electrical signals recorded from the scalp's surface using an electroencephalograph are known as an electroencephalogram (EEG). British physiologist Richard Caton first documented rhythmic brain waves in animal brains in 1875, while German psychiatrist Hans Berger recorded human brain waves for the first time in 1928 [1]. The discovery of brain waves and the development of EEG technology have facilitated precise assessment and quantitative analysis of sleep states, making EEG an invaluable tool in sleep research [2] (Fig. 6.1b).

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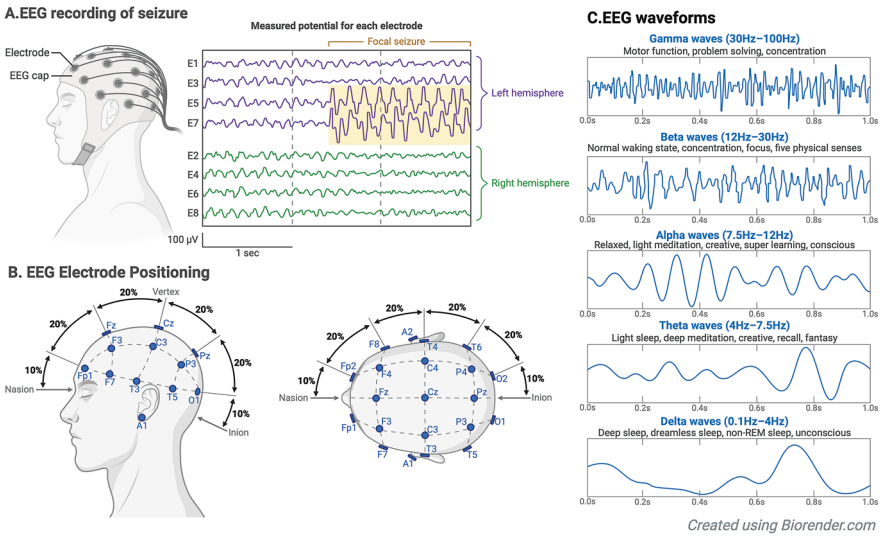

Fig. 6.1 Electroencephalography (EEG) patterns and seizure detection

6.1.1 EEG Waveforms

The primary EEG waveforms include alpha (α), beta (β), theta (θ), and delta (δ) waves (Fig. 6.1c). Alpha waves, with a frequency range of 7.5–12 Hz and amplitude between 20 μV and 100 μV, typically appear as spindle-shaped waves of varying amplitude. They are most prominent in the occipital cortex and are seen in adults who are awake and relaxed and have their eyes closed. When the eyes open or in response to stimuli, alpha waves disappear and are replaced by faster beta waves, a phenomenon known as alpha block. Beta waves range from 12 Hz to 30 Hz in frequency and have an amplitude of 5–20 μV, predominantly observed in the frontal and parietal lobes, indicating heightened neocortical activity.

Theta waves, with frequencies of 4–7.5 Hz and amplitudes of 100–150 μV, are usually seen in adults during drowsiness, especially in the temporal and parietal regions. Delta waves, characterized by a frequency of 0.1–4 Hz and amplitudes of 20–200 μV, typically appear in adults during deep sleep and extreme fatigue or under anesthesia and are most prominent in the temporal and occipital lobes. Additionally, gamma waves with frequencies higher than beta waves (30–100 Hz) can occur during periods of focused attention. Other specific normal brain waves, such as K-complexes, sigma waves, lambda waves, and mu waves, may also be observed during sleep [2].

6.1.2 Variations in EEG Waveforms

In general, brain waves of lower frequencies tend to have higher amplitudes, while those with higher frequencies exhibit lower amplitudes. The characteristics of EEG waveforms can vary significantly depending on the recording site and the individual's condition. During sleep, high-amplitude, slow waves predominate, a state referred to as EEG synchronization. Conversely, during wakefulness, low-amplitude, fast waves are more common, known as EEG desynchronization.

In a state of rest, the primary EEG waveforms change with age. Infants may show rapid beta-like wave activity, whereas slow waves (0.5–2 Hz) are frequently observed in the occipital cortex. As children grow, the slow waves in the occipital cortex gradually increase in frequency, with theta waves becoming evident in early childhood and alpha waves appearing during adolescence. Various physiological conditions can also influence brain wave patterns. Lower levels of blood glucose, body temperature, and glucocorticoids, as well as high levels of arterial blood pressure of carbon dioxide (PCO_2), can slow the frequency of alpha waves, while elevated levels can accelerate them.

In clinical settings, patients with epilepsy or cortical space-occupying lesions, such as brain tumors, may display spike waves (frequency > 12.5 Hz, amplitude 50–150 μV, with steep ascending and descending phases), sharp waves (frequency 5–12.5 Hz, amplitude 100–200 μV, with a steep ascending phase and blunt peak), and spike-and-slow wave complexes (a slow wave following a spike or vice versa, with a slow wave frequency of 2–5 Hz and amplitude 100–200 μV). These waveform changes can assist in diagnosing tumors or epilepsy when evaluated alongside clinical data [3] (Fig. 6.1a).

6.1.3 Mechanisms of EEG Wave Generation

The rhythm of EEG waves is much slower than that of neuronal action potentials, but it is comparable to the time course of postsynaptic potentials. Animal studies have shown that the slow postsynaptic potentials recorded from cortical neurons with microelectrodes are similar to the potential changes observed in EEG recordings from the cortical surface, particularly during wave occurrence. However, the weak postsynaptic potentials of single neurons are insufficient to alter the cortical surface potential significantly. Therefore, it is believed that EEG waves result from the summation of synchronized postsynaptic potentials from numerous neurons. The structural basis for this summation is the orderly arrangement of pyramidal cells in the cortex, with their apical dendrites oriented parallel and perpendicular to the cortical surface, facilitating synchronized activity and generating strong electric fields that affect the surface potential.

The synchronization of widespread cortical neuronal electrical activity is linked to thalamic functionality. In moderately anesthetized animals, spontaneous brain electrical activity with a frequency of 8–12 Hz, similar to alpha waves, can be recorded over large cortical areas. When the fibers connecting the thalamus to the

cortex are severed or the thalamus is removed, this alpha-like rhythm weakens or disappears significantly. However, after cortical removal or severing the thalamocortical fibers, the alpha-like rhythm persists in the thalamic intralaminar nuclei. Electrical stimulation of the thalamic nonspecific projection nuclei at an 8–12 Hz frequency induces alpha-like electrical changes in the cortex. Intracellular recordings from neurons in the thalamic intralaminar nuclei show alternating excitatory and inhibitory postsynaptic potentials (EPSPs and IPSPs) with repeated stimulation, and similar rhythmic potential changes occur in the cortex. Therefore, it is speculated that cortical electrical synchronization results from the alternating EPSPs and IPSPs from the thalamic nonspecific projection nuclei. High-frequency stimulation of the thalamic intralaminar nuclei can transform cortical alpha-like rhythms into desynchronized fast waves, potentially explaining the mechanism behind alpha wave blocking [4].

6.1.4 EEG and Anesthesia Depth

The depth of anesthesia is a state of the central nervous system resulting from the interplay between the suppressive effects of anesthetic drugs and the excitatory effects of nociceptive stimuli. This balance is influenced by the potency of anesthetics, the effectiveness of analgesics, and the intensity of surgical stimuli. Anesthesia profoundly impacts brain electrical activity, leading to significant changes in EEG patterns. Monitoring these EEG alterations provides crucial insights into the patient's brain state during surgery [5]. For example, during light anesthesia, alpha and beta waves may still be present, but as anesthesia deepens, theta and delta waves become more prominent, indicating a deeper level of sedation. Modern anesthesia monitoring systems often use EEG-based indices, such as the bispectral index (BIS), to provide real-time feedback on the patient's level of consciousness [6]. These indices assist anesthesiologists in adjusting the dosage of anesthetic agents to maintain an appropriate depth of anesthesia, ensuring patient safety and optimal surgical conditions.

Accurate assessment and maintenance of appropriate anesthesia depth are essential in clinical practice. This aligns with the American Society of Anesthesiologists' (ASA) goals for anesthesia, which include avoiding intraoperative awareness, ensuring optimal recovery from anesthesia, maintaining ideal hemodynamics, preventing postoperative cognitive dysfunction, and reducing postoperative mortality. Tools like the bispectral index (BIS) and Narcotrend are commonly used to monitor anesthesia depth, with these EEG analysis metrics correlating well with sedation levels.

- **Bispectral Index**
  The bispectral index (BIS) combines power spectrum, frequency spectrum analysis, and EEG-related function spectrum analysis, integrating various EEG variables into a single value ranging from 0 to 100, with lower values indicating deeper cerebral inhibition. A BIS value of 100 represents an awake state, and 0

indicates no EEG signal. Suitable anesthesia depth is maintained at BIS values between 40 and 60. Approved by the FDA in 1997 for monitoring anesthesia depth and sedation levels, BIS has been used in millions of clinical anesthesia cases.

BIS reflects cortical electrical activity and correlates well with sedation levels but has limitations. Insufficient analgesia can lead to hemodynamic fluctuations and increased BIS values during intense nociceptive stimuli. BIS is also sensitive to electromyographic activity, gradually increasing as muscle relaxation decreases. Therefore, BIS monitoring can predict the adequacy of analgesic and muscle relaxant use to some extent. Satisfactory anesthesia depth requires appropriate levels of sedatives, analgesics, and muscle relaxants. Since the central nervous system for movement and autonomic responses to noxious stimuli is located in the spinal cord or brainstem, BIS is not a reliable predictor of noxious stimulus response. Combining BIS with vital signs monitoring may more accurately guide anesthesia to prevent intraoperative awareness and noxious stimulus responses [7].

- **Narcotrend Monitor**
  Narcotrend (NT) is a new EEG/consciousness depth monitoring system with specialized EEG signal collection amplifiers, capable of real-time accurate monitoring of EEG signals collected from any location on the brain using standard ECG electrodes. It provides specific consciousness classification stages (Narcotrend stages, NTS), dividing EEG into six stages and 15 levels from A (awake) to F (no EEG activity), displayed as 0 (isoelectric) to 100 (awake) on the Narcotrend index (NI). Suitable anesthesia depth should be maintained in stages D to E. The latest software provides a dimensionless anesthesia depth index (NI) from 0 to 100 for easier clinical application [8].

6.2 Evoked Potentials

Cortical evoked potentials refer to electrical changes in specific cortical regions triggered by sensory input or stimulation of particular brain areas. These potentials can be elicited by activating receptors, sensory nerves, or any part of the sensory pathway. Evoked potentials typically include primary responses, secondary responses, and afterdischarges [9].

- **Primary Responses**
  The primary response is a distinctive potential change with a specific cortical center and a latency period determined by factors such as the distance between the stimulation site and the cortex, nerve conduction speed, and the number of synapses. This response is linked to the activity of the specific sensory projection system.
- **Secondary Responses**
  Secondary responses are follow-up, widespread reactions observed in extensive cortical areas, not directly tied to the timing of the initial stimulation. These are associated with nonspecific sensory projection system activity.

- **Afterdischarges**
  Afterdischarges involve periodic potential fluctuations that occur following the primary and secondary responses. These result from the depolarization and hyperpolarization of apical dendrites due to nonspecific sensory input and intermediary neurons.

Evoked potentials are often masked by ongoing spontaneous brain activity, making them challenging to distinguish. However, electronic computers can average and process these potentials, allowing them to stand out clearly as averaged evoked potentials. These averaged potentials are invaluable for studying sensory functions, neurological conditions, behavior, and psychological activities [10].

In clinical settings, evoked potentials are commonly used in various diagnostic and research applications:

- **Somatosensory evoked potentials (SEP):** SEPs are generated by stimulating a limb and recording the resulting potentials from the contralateral cortical sensory projection area.
- **Auditory evoked potentials (AEP):** AEPs are elicited by brief auditory stimuli, recorded from scalp areas corresponding to the temporal cortex.
- **Visual evoked potentials (VEP):** VEPs are triggered by brief light stimuli and recorded from scalp areas over the occipital cortex.

Advances in signal processing techniques have further enhanced the utility of evoked potentials [11]. Techniques such as time-frequency analysis and wavelet transforms allow for more precise characterization of these potentials, providing deeper insights into the functional state of the brain. Ongoing research is focused on improving the sensitivity and specificity of evoked potential measurements. The integration of machine learning algorithms with evoked potential analysis holds promise for more accurate diagnoses and personalized treatment plans.

6.2.1 AEP and Anesthesia Depth

During the induction of general anesthesia, auditory perception is the last sense to be lost and the first to return, with its suppression indicating deeper levels of anesthesia. The AEP index measures electrical activity from the auditory system, spanning from the cochlea to various auditory centers, and consists of three components: brainstem auditory evoked potentials (BAEP or short-latency AEPs within 10 milliseconds poststimulation), mid-latency AEPs (MLAEPs within 10–100 milliseconds poststimulation), and long-latency AEPs (more than 100 milliseconds poststimulation). MLAEPs, primarily originating from the medial geniculate body and primary auditory cortex, exhibit dose-dependent changes with most anesthetics (excluding ketamine and diazepam) and are useful for monitoring intraoperative awareness [12].

The AEP index ranges from 0 to 100 to indicate the depth of anesthesia and sedation, with 60–100 representing an awake state, 40–59 indicating sedation, 30–39 signifying light anesthesia, and below 30 indicating deep anesthesia. Research has demonstrated that patients under surgical anesthesia with suppressed implicit memory formation also had significantly reduced MLAEPs. Consequently, MLAEPs can predict the effects of auditory stimuli on implicit memory during surgery [13].

6.2.2 SEP for Spinal Cord Monitoring

Monitoring spinal cord function is critical in many spinal surgeries, often utilizing SEPs. Changes in SEP amplitude and latency can indicate spinal cord injury. Potent inhalation anesthetics significantly prolong SEP latency and decrease amplitude, with greater suppression at higher concentrations. In contrast, intravenous anesthetics have a smaller impact on SEPs, and anesthesia with nitrous oxide, fentanyl, and muscle relaxants does not affect SEPs. The effects of controlled hypotension and moderate hypothermia on SEPs are not well defined, but severe hypotension and shock significantly suppress SEPs. SEPs primarily reflect dorsal spinal cord function, while reduced blood flow in the anterior spinal artery can lead to ventral spinal cord ischemia, which may not always be detected by SEPs.

In spinal surgery, SEP monitoring helps detect and prevent potential spinal cord injuries, allowing for timely intervention. This is particularly important in procedures involving spinal deformity correction or tumor resection, where the risk of spinal cord damage is high [14].

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Effects of Anesthetics on the Central Nervous System

7

Anesthesia profoundly affects the central nervous system (CNS), shaping the practice of modern medicine by enabling complex surgical procedures while minimizing patient discomfort and awareness. The pharmacodynamic and pharmacokinetic properties of anesthetics influence cerebral physiology, including blood flow, metabolism, and neuronal activity, which have significant implications for both neuroprotection and neurotoxicity. Understanding these effects is crucial for tailoring anesthesia to individual patients, particularly in neurosurgical and critical care settings. This chapter provides an in-depth exploration of the mechanisms and clinical applications of various anesthetics, including inhalation agents, intravenous drugs, intrathecal techniques, and adjunctive medications. The discussion emphasizes their impact on CNS function, cerebral autoregulation, and intracranial dynamics, with a focus on optimizing outcomes in diverse clinical scenarios.

7.1 Inhalation Anesthetics

Inhalation anesthesia utilizes gases or vapors that are absorbed through the respiratory system to induce anesthesia. These volatile anesthetics are categorized into three groups: hydrocarbon ethers, halogenated hydrocarbon ethers, and halogenated hydrocarbons. Hydrocarbon ethers include agents like diethyl ether, divinyl ether, and ethyl vinyl ether. The halogenated hydrocarbon ethers category comprises methoxyflurane, enflurane, isoflurane, sevoflurane, and desflurane, while halogenated hydrocarbons include halothane, trichloroethylene, and chloroform [1]. Gas anesthetics include nitrous oxide, ethylene, and cyclopropane. These substances induce anesthesia by being absorbed and distributed throughout the body, leading to loss of sensation [2]. Comprehending the pharmacokinetics of these anesthetics is crucial for understanding their induction, maintenance, and recovery phases. The primary objective of administering inhalation anesthetics is to sustain an adequate partial pressure of the anesthetic in the brain, ensuring the patient remains unconscious throughout the surgical procedure [3].

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7.1.1 Nitrous Oxide

Nitrous oxide is known for its relatively weak anesthetic properties. Inhaling 30–50% nitrous oxide yields analgesic effects, whereas concentrations exceeding 80% induce anesthesia. The minimum alveolar concentration (MAC) for nitrous oxide is 105. Although the dose-response relationship of nitrous oxide on cerebral blood flow remains debated, concentrations of 60–70% can cause cerebral vasodilation and increased intracranial pressure. The impact of nitrous oxide on brain metabolism is also controversial, potentially due to the influence of pre-administration of other drugs affecting cerebral blood flow and metabolism, as well as species differences [4]. Pre-administration of diazepam or thiopental can block the increase in intracranial pressure induced by nitrous oxide, with clinical outcomes being more influenced by premedication and combination therapy. Animal studies indicate that, without premedication, nitrous oxide can increase cerebral blood flow by 150% within 5 min, with this effect lasting nearly an hour. This increase primarily occurs in the cerebral cortex, with a corresponding 150% increase in oxygen metabolism. In patients with elevated intracranial pressure, inhaling 50% or higher concentrations of nitrous oxide can lead to clinically significant increases in intracranial pressure. Therefore, caution is advised when using nitrous oxide in neurosurgical patients with reduced intracranial compliance.

Inhaling 50–70% nitrous oxide can induce loss of consciousness, disappearance of alpha rhythms in the electroencephalogram (EEG), and the emergence of fast waves superimposed on delta waves. When the concentration reaches 80% and is combined with muscle relaxants, the EEG exhibits 4–6 Hz slow waves [5].

7.1.2 Halothane

Halothane is a highly effective inhalation anesthetic known for its strong central nervous system depressant effects but minimal analgesic properties. As halothane concentration rises, cerebral blood flow also increases, up to the point where systemic hypotension lowers cerebral perfusion pressure below the autoregulation threshold. Due to variations in species and experimental setups, pinpointing the precise dose-response curve for halothane's impact on brain metabolism is challenging [6]. Research on animals indicates that 1% halothane can decrease cerebral oxygen metabolism by 25%. At concentrations ranging from 2.3% to 9%, each 1% increment causes a 15% reduction in cerebral oxygen metabolism, until the EEG becomes isoelectric. At very high levels, halothane can induce reversible disturbances in brain energy metabolism and lactic acidosis. Concentrations of 4–5% can lead to an isoelectric EEG, with dose-dependent changes apparent before reaching this point. In subanesthetic conditions, the EEG displays sinusoidal waves of 12–18 Hz; at 1 MAC, waves of 11–16 Hz are seen; and with each 0.5 MAC increase, the frequency decreases by 1 Hz [7]. Halothane also induces dose-related changes in evoked potentials, with cortical evoked potentials being more sensitive to anesthetics than brainstem potentials.

7.1.3 Enflurane

With rising enflurane blood concentrations, central nervous system suppression intensifies, resulting in high-voltage slow waves on the EEG. Inhaling 3–3.5% enflurane can lead to significant central nervous system depression accompanied by seizure-like spike waves, either single or repetitive. Clinically, this might manifest as tonic-clonic muscle contractions in the face and limbs [8]. Enflurane increases evoked responses to visual and auditory stimuli on the EEG, with seizure-like spikes becoming prominent under deep enflurane anesthesia, especially when $PaCO_2$ is lower than normal. Elevating $PaCO_2$ raises the spike threshold, so reducing anesthesia depth and increasing $PaCO_2$ can swiftly eliminate these motor responses. In children, inhaling 3% enflurane with moderate $PaCO_2$ reduction can induce epileptic EEG activity [9]. However, both clinical and animal studies have indicated that enflurane does not cause long-lasting changes in the central nervous system.

During enflurane anesthesia, if arterial pressure remains stable, cerebral vasodilation occurs, increasing cerebral blood flow and intracranial pressure. Enflurane is a strong cerebral depressant; deeper anesthesia leads to larger reductions in cerebral oxygen consumption. Inhaling 3% enflurane cuts central oxygen consumption by 50%. While enflurane anesthesia may show epileptiform activity, the metabolic rate only rises to nearly pre-anesthetic levels.

7.1.4 Isoflurane

Isoflurane's effect on brain physiology is notable for its dose-related changes. At 1 MAC, there is an increase in both frequency and amplitude of EEG waves [10]. Beyond this concentration, amplitude continues to rise, while frequency falls. In deeper stages of anesthesia, both frequency and amplitude diminish. Burst suppression is seen at 1.5 MAC, with isoelectric waves occurring at 2 MAC. Isoflurane, unlike enflurane, does not induce convulsions even with deep anesthesia, low $PaCO_2$, or auditory stimulation. Isoflurane at 0.6–1.1 MAC does not cause a rise in cerebral blood flow, whereas at 1.6 MAC, it doubles, albeit less significantly than with halothane, leading to a smaller increase in intracranial pressure. In craniotomy patients, isoflurane under low $PaCO_2$ conditions can prevent the increase in intracranial pressure, a challenge when using halothane or enflurane [11].

7.1.5 Sevoflurane

Administering 4% sevoflurane via an oxygen mask for 2 min results in loss of consciousness. The EEG initially displays rhythmic slow waves, which progressively diminish with deeper anesthesia, eventually showing spike-wave patterns akin to those observed with barbiturates. A slower induction using 1% sevoflurane over a 10-min period does not lead to unconsciousness or EEG alterations. Sevoflurane acts on the midbrain reticular formation, inhibiting neuronal activity in a

dose-responsive manner. Although deep sevoflurane anesthesia can induce generalized seizures, this occurs less frequently than with enflurane, reducing clinical concerns.

Sevoflurane exhibits a dose-dependent cerebral vasodilatory effect, though this effect is milder compared to halothane, isoflurane, or desflurane. In animal studies, sevoflurane has been shown to increase intracranial pressure and decrease oxygen metabolism in a dose-dependent manner without significantly altering cerebral blood flow. In cats, sevoflurane markedly increases intracranial pressure, whereas in dogs with normal intracranial compliance, the effect is minimal. Clinical trials confirm that sevoflurane acts as a cerebral vasodilator, leading to dose-dependent increases in cerebral blood flow [12]. At a concentration of 1.5%, sevoflurane does not significantly impact cerebral blood flow, intracranial pressure, cerebrovascular resistance, or cerebral oxygen metabolism. At concentrations between 1.5% and 2.5%, sevoflurane significantly reduces cerebrovascular resistance, but the resulting increase in cerebral blood flow does not elevate intracranial pressure, and cerebral oxygen metabolism remains stable. The cerebral vascular response to carbon dioxide remains intact [13].

7.1.6 Desflurane

Desflurane exerts its effects on the central nervous system in a dose-dependent fashion. At concentrations within 1 MAC, both the frequency and amplitude of brain waves increase. Beyond this threshold, the amplitude continues to rise, but the frequency diminishes; in deep anesthesia, both parameters decrease. Burst suppression is observed at 1.5 MAC, and isoelectric activity appears at 2 MAC. Unlike enflurane, deep anesthesia with desflurane, low PaCO2, or auditory stimulation does not trigger convulsions.

Desflurane's ability to inhibit metabolism and dilate cerebral blood vessels enhances oxygen delivery to brain tissue, thereby alleviating hypoxia caused by arterial blockage. It has a pronounced dose-dependent vasodilatory effect on cerebral vessels, which increases cerebral blood flow and raises intracranial pressure. Desflurane reduces cerebral oxygen metabolism in a dose-responsive manner, similar to halothane and isoflurane, affecting the coupling between cerebral blood flow and metabolism. Like isoflurane, desflurane maintains the brain's sensitivity to carbon dioxide levels. It significantly suppresses brain function, inducing early burst suppression on EEG, comparable to isoflurane. Although desflurane-induced cerebral vasodilation can increase intracranial pressure in susceptible individuals, appropriate anesthesia depth and hyperventilation can mitigate this effect in patients with compromised intracranial compliance.

For individuals without intracranial pathology, rapid induction with desflurane at concentrations above 0.5 MAC can disrupt both static and dynamic cerebral autoregulation, whereas isoflurane at 1.5 MAC or higher preserves these functions. Administering desflurane alone for induction can elevate heart rate, blood pressure,

and cerebral blood flow, making it less suitable for patients with reduced intracranial compliance.

At 1 MAC, desflurane inhibits brain metabolism similarly to other anesthetics but more significantly decreases cerebral oxygen metabolism. This reduction in metabolic rate is primarily due to the anesthetic's suppression of brain activity and sympathetic nervous system inhibition, offering some degree of cerebral protection [4, 7].

7.2 Intravenous Anesthetics

7.2.1 Barbiturates

Barbiturates are believed to exert their effects primarily through interaction with γ-aminobutyric acid (GABA) receptors. GABA is the main inhibitory neurotransmitter in the central nervous system, and its receptors are oligomeric structures composed of at least five protein subunits. These receptors form GABA-associated chloride ion channels and have binding sites for various substances, including barbiturates, benzodiazepines, steroids, and picrotoxin. Activation of GABA receptors enhances chloride ion conductance through these channels, leading to hyperpolarization of the neuronal membrane and inhibition of postsynaptic neuron activity. Therefore, GABA receptors function as ligand-gated chloride ion channels [7]. Barbiturates both enhance and mimic GABA's effects. By binding to these receptors, barbiturates decrease the rate at which GABA dissociates from the receptors, extending the frequency and duration of chloride ion channel opening. At slightly higher than therapeutic concentrations, barbiturates can directly activate chloride ion channels even without GABA, intensifying GABA's effects and causing sedative and hypnotic outcomes. At elevated concentrations, their GABA-mimetic action results in anesthesia [14].

Thiopental primarily affects the cerebral cortex and reticular formation, suppressing the ascending reticular activating system and decreasing cortical excitability by directly impacting multisynaptic transmission in the cortex. Its effects on the cerebellum, vestibular system, and spinal cord are less pronounced. Intravenous administration of thiopental induces unconsciousness within 15–30 seconds, with peak effects occurring around 1 min and the sleep duration lasting approximately 15–20 mins. Post-awakening, sleep may persist for an additional 3–5 h. EEG patterns during thiopental-induced anesthesia resemble those of natural sleep, transitioning from alpha waves to high-amplitude, low-frequency delta and theta waves, followed by burst suppression and flatline, with normal recovery taking up to 48 h. Thiopental inhibits the cerebral metabolic rate of oxygen ($CMRO_2$) in a dose-dependent manner, with maximal inhibition (55%) observed when the EEG shows a flatline, indicating reduced neuronal oxygen consumption rather than metabolic suppression. Both cerebral blood flow and intracranial pressure decline in parallel, with reductions of approximately 48% and 50%, respectively. This decrease in intracranial pressure could be beneficial in neurosurgical settings, especially in

cases of brain herniation or increased intracranial pressure induced by ketamine or halothane, although the effect is transient, lasting only 3–7 mins in some instances, and does not affect normal intracranial pressure [15]. Respiratory depression during thiopental administration can lead to CO_2 accumulation, which increases cerebral blood flow and raises intracranial pressure. Additionally, thiopental elevates the excitation threshold of cortical neurons, providing anticonvulsant properties.

At subanesthetic doses, thiopental can cause hyperalgesia, increasing sensitivity to painful stimuli without memory of the pain due to its amnesic effects. Hyperalgesia is characterized by symptoms such as tachycardia, increased muscle tone, sweating, tearing, and rapid breathing. However, in healthy individuals, intravenous administration of sedative doses of thiopental does not induce hyperalgesia during heat pain stimulation. Patients emerging from thiopental anesthesia may experience increased pain perception, potentially lasting longer, possibly due to concurrent inhibition of the reticular formation's pain inhibitory pathways [16].

7.2.2 Opioid Drugs

Opioid drugs achieve their effects through intricate interactions with opioid receptors, which are G-protein-coupled receptors (GPCRs) located on the surfaces of certain cells in both the central and peripheral nervous systems. The primary types of opioid receptors include Mu (μ) receptors, delta (δ) receptors, and kappa (κ) receptors. When opioids bind to these receptors, they activate several intracellular signaling pathways, leading to a series of events. One key effect is the inhibition of adenylyl cyclase, which reduces cAMP levels and decreases the activity of protein kinase A (PKA). This reduction in PKA activity leads to decreased phosphorylation of various target proteins involved in pain transmission [17]. Opioid receptor activation also affects pain modulation through the activation of potassium channels and inhibition of calcium channels. The opening of potassium channels causes an efflux of K^+ ions, hyperpolarizing the cell membrane and reducing the likelihood of action potentials. Simultaneously, the inhibition of calcium channels reduces Ca^{2+} influx, leading to decreased release of neurotransmitters, including those involved in pain signaling. These combined effects on pain pathways and neurotransmitter release enable opioids to provide effective analgesia. However, their use is accompanied by significant risks, including side effects, tolerance, dependence, and addiction [18].

A dose of 1 mg/kg morphine combined with 70% nitrous oxide maintains cerebral arterial autoregulation. When the dose is increased to 3 mg/kg with the same concentration of nitrous oxide, there is a slight reduction in cerebral blood flow and a minor decrease in metabolic activity. Meperidine and fentanyl at equivalent doses with 70% nitrous oxide produce comparable effects. Opioid-induced changes in cerebral blood flow and metabolism can be reversed with opioid antagonists.

Opioids as premedication have a minimal impact on the EEG. Large doses of morphine (1–2 mg/kg) or meperidine (5–10 mg/kg) may reduce alpha frequency moderately. In animal studies, high doses of fentanyl have induced epileptic activity in rats, but this has not been observed clinically in humans.

- **Morphine**
  Research specifically on morphine's impact on cerebral blood flow and metabolism is limited. A 1 mg dose of morphine does not change cerebral blood flow, but it decreases cerebral oxygen metabolism by 40% [19]. Most studies examine morphine's effects when combined with other anesthetics. When combined with 70% nitrous oxide, doses of 1–3 mg/kg morphine do not significantly affect cerebral blood flow and metabolism. Morphine can cause histamine release, leading to cerebral vasodilation and increased cerebral blood volume, with cerebral blood flow influenced by arterial pressure. Combining 2 mg morphine with 70% nitrous oxide maintains cerebral autoregulation within a mean arterial pressure range of 60–120 mmHg.
- **Fentanyl**
  Data on fentanyl's effects on human cerebral blood flow and metabolism are scarce. Evidence indicates that fentanyl moderately reduces cerebral blood flow and metabolism. Large doses of fentanyl do not affect the autoregulation of cerebral blood flow in dogs compared to barbiturate anesthesia or alter cerebral blood flow's sensitivity to $PaCO_2$ changes. Fentanyl anesthesia also maintains the brain's hyperemic response to hypoxia.
- **Alfentanil**
  In barbiturate-anesthetized dogs, 320 μg/kg alfentanil does not affect cerebral blood flow, metabolism, cerebrovascular response to CO_2, or cerebral autoregulation. There is a lack of clinical data on patients.
- **Sufentanil**
  Sufentanil reduces cerebral blood flow and metabolism in a dose-dependent manner. In patients with elevated intracranial pressure, 1–2 μg/kg sufentanil can lower intracranial pressure.
- **Remifentanil**
  Remifentanil's impact on cerebral blood flow and metabolism is minimal, consistent with other opioids.

Opioids, particularly morphine and fentanyl, have been studied for their potential neuroprotective effects [20]. Some research suggests that opioids may reduce neuronal injury by modulating glutamate release and inhibiting excitotoxicity. This neuroprotective mechanism can be beneficial during episodes of cerebral ischemia or traumatic brain injury. However, opioids can also pose a risk of neurotoxicity, particularly with prolonged use or high doses, leading to concerns about their impact on long-term cognitive function. Genetic factors, age, and the presence of comorbidities can influence individual responses to opioids. Polymorphisms in opioid receptor genes and enzymes involved in opioid metabolism can result in variability in efficacy and side effects. Personalized approaches to opioid administration, considering these individual differences, can improve patient outcomes and reduce the risk of adverse effects.

7.2.3 Propofol

Propofol primarily enhances the activity of GABA receptors, thereby increasing inhibitory neurotransmission which leads to sedation, hypnosis, and amnesia. Its rapid onset and brief duration make it particularly effective for both the induction and maintenance of anesthesia in various clinical settings [12]. Widely used for its hypnotic, sedative, and amnesic effects, propofol has minor analgesic properties. Unlike thiopental, it does not have antianalgesic effects, and subhypnotic doses do not increase pain sensitivity, making it ideal for sedation.

During surgical procedures, propofol is typically administered rapidly via intravenous infusion to maintain anesthesia. Without external stimuli, a continuous infusion rate of at least 2 mg/kg/h is necessary to maintain amnesia and prevent awakening, with blood levels surpassing 2 μg/ml. Postoperatively, patients generally wake calmly, though some may experience hallucination, sexual fantasies, or opisthotonos. Emotional changes are less frequent than with thiopental anesthesia. Myoclonic phenomena, while more frequent with propofol than with thiopental, occurs less common compared to etomidate or methohexital.

EEG changes during propofol anesthesia resemble those of other intravenous anesthetics. An initial intravenous injection of 2.5 mg/kg propofol followed by continuous infusion first increases alpha rhythms, followed by gamma and theta frequencies, with rapid infusion causing burst suppression. EEG power analysis shows increased amplitude at blood concentrations of 3–8 μg/ml, while levels above 8 μg/ml lead to significant amplitude reduction and burst suppression [20]. The bispectral index (BIS), which measures central sedation levels, correlates well with blood propofol levels, with values above 90 indicating wakefulness and values near 0 indicating deep anesthesia. During propofol anesthesia, BIS values decrease in a dose-dependent manner. BIS values of 63 and 51, 50% and 95% of patients, respectively, being unresponsive to verbal commands, while at 77, 95% of patients have no recall. The BIS curve during propofol anesthesia mirrors those of isoflurane and midazolam, with values near 50 or slightly lower indicating loss of consciousness in 95% of subjects [21].

Propofol also exhibits anticonvulsant properties, making it useful for managing seizures. While it does not affect brainstem auditory evoked potentials (BAEPs), it prolongs latency and reduces the amplitude of cortical mid-latency auditory potentials. Notably, once an unresponsive state is achieved with propofol, auditory evoked potential index may show sudden changes, whereas BIS consistently decreases with deepening sedation and loss of consciousness [22].

In terms of intracranial effects, propofol effectively reduces intracranial pressure (ICP) in patients, whether their intracranial pressure is normal or elevated, thus proving beneficial for intracranial surgeries [23]. In patients with normal ICP, a reduction of about 30% is typically seen, mostly due to decreased cerebral perfusion pressure. In cases of elevated ICP, the reduction can range from 30% to 50%, which may carry risks due to significant decrease in both cerebral perfusion pressure and cerebral blood flow. During tracheal intubation, small doses of fentanyl or additional propofol can mitigate reactive ICP increases. Throughout propofol infusion,

cerebrovascular responses to CO_2 and autoregulation remain intact, and it provides cerebral protection during acute brain ischemia by reducing cerebral oxygen metabolism, similar to the effects of halothane and thiopental. However, its depressant effects on circulation and respiration raise concerns regarding its use in cerebral resuscitation after circulatory arrest.

In contrast to ketamine, which increases intraocular pressure (IOP), propofol significantly reduces IOP by 30–40%, even more effectively than thiopental. This characteristic makes it particularly useful for preventing pressure increases during succinylcholine administration and tracheal intubation, thereby offering an additional benefit in managing patients undergoing such procedures [24].

7.2.4 Ketamine

Ketamine induces a distinct type of anesthesia known as a dissociative state, which is markedly different from traditional anesthetics. Instead of producing a natural sleep-like state, ketamine results in a catatonic condition where patients keep their eyes open and maintain reflexes such as corneal, coughing, and swallowing. However, these reflexes do not offer any protective function. Although patients remain unaware of the surgical procedure, the amnesic effects of ketamine are less pronounced compared to benzodiazepines. Consciousness is entirely absent, but muscle tone increases, and the eyes may appear fixed or show nystagmus. This state, characterized by superficial anesthesia with effective analgesia for surface pain but inadequate relief for deeper pain, is termed dissociative anesthesia. Even with good surface pain management, abdominal surgeries involving visceral traction can elicit responses [25].

During ketamine anesthesia, some individuals may experience increased tearing and salivation, along with hyperactive reflexes such as knee jerks, Achilles tendon reflexes, and H reflexes. Research on evoked potentials indicates that visual and somatosensory stimuli reach the cortical sensory areas, but the brain cannot process these inputs, leading to an inability to respond appropriately to light or painful stimuli [26]. Patients may also exhibit increased skeletal muscle tone, occasionally clenching their teeth or displaying involuntary limb movements, known as a cataleptic state or catatonia, which is a hallmark of ketamine anesthesia [27].

Ketamine predominantly impacts the brain's associative networks while leaving the brainstem reticular activating system intact. Although sensory inputs reach the cortex, they are not consciously perceived due to the suppression of associative areas by ketamine. Animal research has shown that ketamine anesthesia abolishes evoked potentials from electrical stimulation of the midbrain reticular formation, pain, and light stimuli. This implies that ketamine acts on the diffuse thalamocortical projection system, inhibiting impulses transmitted through the reticular formation and thalamus. Additionally, ketamine obstructs electrical potentials induced by painful dental pulp stimulation in cortical somatosensory areas, nonspecific thalamic nuclei, and the midbrain reticular formation, indicating its role in hindering pain transmission to the thalamus and cortex. Ketamine's analgesic properties are

due to the disruption of nonspecific midbrain and thalamic pathways. Furthermore, ketamine activates the limbic system while suppressing the thalamocortical system, leading to functional dissociation. This limbic system excitation can result in heightened emotional activity during recovery. EEG shows suppression of alpha rhythms, synchronous high delta waves in the thalamocortical system, and slow theta waves in the hippocampus and limbic system, which supports this theory.

During ketamine anesthesia, there is excitation of the medulla and limbic system, while the thalamus experiences inhibition. This selective pattern of excitation and inhibition results in sensory dissociation from the surroundings, emotional activities disconnected from consciousness, superficial anesthesia with profound analgesia, and unrecognized sensory transmission. These contrasting effects give rise to the term dissociative anesthesia, though it may be debated due to variations in excitation and inhibition levels or a possible dulled response from the limbic system.

Ketamine acts as a nonspecific N-methyl-D-aspartate (NMDA) receptor antagonist in the central nervous system, producing general anesthesia by blocking excitatory neurotransmission at NMDA receptors. This action inhibits glutamate, the primary excitatory neurotransmitter in the central nervous system, leading to reduced calcium ion influx into neurons and decreased neuronal excitability and synaptic transmission. Additionally, ketamine interacts with opioid receptors, particularly binding to the μ-opioid receptors through its S(+)-isomer, which contributes to its analgesic properties. It also affects the monoaminergic system and indirectly influences GABA receptors. These combined interactions reduce excitatory neurotransmission and modulate various neurotransmitter systems, enhancing ketamine's effectiveness as an anesthetic. Evidence suggests that ketamine's spinal analgesia is linked to the inhibition of wide dynamic range neuronal activity. While some drugs can counteract ketamine's effects, no specific receptor antagonist fully reverses all its central actions [28].

Ketamine increases cerebral blood flow, which leads to elevated intracranial pressure and cerebrospinal fluid pressure. It also raises cerebral metabolism and $CMRO_2$. EEG shows theta waves, indicative of analgesia. In patients with elevated intracranial or cerebrospinal fluid pressure, ketamine should only be used with continuous monitoring and rapid intervention for pressure relief [29]. Pre-administration of thiopental or diazepam can block ketamine-induced increases in cerebral blood flow and intracranial pressure. Despite its effects on cerebral dynamics, ketamine does not impair the brain's vasodilatory response to CO_2, allowing hyperventilation to counteract increased intracranial pressure. Ketamine also raises intraocular pressure, peaking at 15 mins postinjection and returning to baseline by 30 min. Therefore, it is contraindicated in patients with glaucoma [30].

7.2.5 Etomidate

Etomidate has a rapid onset similar to that of thiopental and methohexital, inducing sleep almost immediately after administration, typically within one arm-brain circulation time. It is significantly more potent than thiopental by approximately 12 times

and four to five times more potent than methohexital. Induction with etomidate is smooth, comfortable, and generally free from excitement or agitation, often accompanied by amnesia.

For unanesthetized adults, the minimum anesthetic dose is around 0.25 mg/kg, although the clinically recommended dose is 0.3 mg/kg. Within the clinical dose range of 0.1–0.4 mg/kg, patients awaken naturally within 7–14 mins, which is slightly faster than methohexital and much quicker than thiopental. Etomidate does not provide analgesic effects. During maintenance of anesthesia, the plasma concentration of the drug hovers between 300 and 500 ng/ml, with sedation levels at 150–300 ng/ml and waking concentrations at 150–250 ng/ml. Although the precise mechanism of action remains unclear, the fact that GABA antagonists can counteract etomidate's effects suggests its interaction with the GABAergic system [31].

Etomidate decreases cerebral blood flow by 34% and reduces the $CMRO_2$ by 45%, all without influencing mean arterial pressure. This helps maintain or slightly enhance cerebral perfusion pressure, thereby improving the brain's oxygen supply-demand balance. In patients with elevated intracranial pressure, etomidate anesthesia can lower intracranial pressure by up to 50% when the EEG shows burst suppression. Unlike thiopental, etomidate does not reduce mean arterial pressure when decreasing intracranial pressure. Cerebrovascular reactivity is preserved during etomidate anesthesia, allowing for hyperventilation to further reduce intracranial pressure [32].

The EEG changes observed during etomidate anesthesia are akin to those seen with thiopental: an initial increase in alpha wave amplitude, followed by bursts of beta waves, and then mixed delta-theta waves, with delta waves becoming predominant before burst suppression occurs. Etomidate increases epileptic activity in seizure-prone areas on the EEG, which can be helpful for surgical localization of epileptic foci. The initial EEG excitation seen with etomidate administration is similar to methohexital and often requires premedication with opioids to mitigate this effect. Etomidate's impact on auditory evoked potentials mirrors that of inhalation anesthetics, prolonging latency and reducing the amplitude of the initial cortical components, while brainstem evoked potentials remain unaffected. When monitoring transcranial motor evoked responses, the mild EEG suppression caused by etomidate is more favorable compared to propofol [6, 33].

7.3 Muscle Relaxants

Muscle relaxants, though not directly acting on cerebral blood vessels, exert significant indirect effects on patients undergoing neurosurgery. They can lower central venous pressure, reduce resistance to cerebral venous return, and subsequently decrease intracranial pressure. However, in cases where cerebral autoregulation is compromised, these agents can elevate intracranial pressure by increasing arterial pressure. Some relaxants also release histamine, which can decrease cerebral perfusion pressure. The choice of muscle relaxant should be guided by the patient's specific pathophysiological state, the cardiovascular impacts of the muscle relaxant,

and its potential to release histamine. For instance, succinylcholine has been noted to elevate intracranial pressure; however, this is often attributed to inadequate anesthesia depth and improper technique. Administering thiopental and inducing hyperventilation can typically prevent significant rises in intracranial pressure [34].

- **Non-depolarizing Muscle Relaxants**
  These agents may influence cerebral blood vessels indirectly through the release of histamine. Histamine can lower mean arterial pressure, which in turn reduces cerebral perfusion pressure while potentially increasing intracranial pressure due to cerebral vasodilation [34]. In the presence of an intact blood-brain barrier, it is uncertain whether these effects are a direct result of histamine action on cerebral vessels or secondary to decreased mean arterial pressure. Among non-depolarizing muscle relaxants, tubocurarine is known for its strong histamine release [6]. However, modern non-depolarizing agents like pancuronium, atracurium, and vecuronium have minimal histamine release [35].
  The indirect effects of non-depolarizing muscle relaxants on cerebral physiology are typically observed under abnormal conditions or at high doses. These relaxants help reduce intracranial pressure by inhibiting muscle activities such as coughing and breath-holding. Thus, most non-depolarizing muscle relaxants can be safely used in patients with elevated intracranial pressure, as long as they are administered in appropriate doses and at a controlled rate to avoid hypotension and significant histamine release [2, 6].
- **Depolarizing Muscle Relaxants**
  When anesthesia is not sufficiently deep, the use of succinylcholine can lead to an elevation in intracranial pressure. However, the muscle fasciculations caused by succinylcholine are not a major factor in this increase. To prevent this adverse effect, it is effective to deepen the level of anesthesia or to administer non-depolarizing muscle relaxants beforehand [34]. By ensuring the patient is adequately anesthetized and managing stress responses—such as controlling $PaCO_2$ and maintaining stable blood pressure—succinylcholine remains a viable option for induction in neurosurgical procedures. Additionally, proper anesthesia depth and premedication strategies can mitigate the rise in intracranial pressure, making succinylcholine safe and effective for use in neurosurgical patients [2].

7.4 Intrathecal Anesthetics

7.4.1 Subarachnoid Block and Mechanisms

Intrathecal anesthesia involves the administration of local anesthetics into specific compartments within the spinal canal to achieve regional anesthesia. This technique includes subarachnoid block anesthesia and epidural block anesthesia. Both methods are used to block nerve transmission and provide pain relief for surgeries and other procedures [6, 36].

Subarachnoid block anesthesia involves injecting local anesthetics directly into the cerebrospinal fluid (CSF) within the subarachnoid space via a lumbar puncture. Although some anesthetics may diffuse to the surface of the spinal cord, their primary action is to block the spinal nerve roots. This form of anesthesia interrupts the transmission of afferent impulses entering the central nervous system through the dorsal roots and efferent impulses exiting via the ventral roots [6].

Research by Cohen, using ^{14}C-labeled procaine or lidocaine injected into the subarachnoid space, revealed that both the spinal nerve roots and the spinal cord absorb these local anesthetics [37]. The concentration of anesthetics is notably higher in the dorsal roots compared to the ventral roots. This is significant because the dorsal roots contain unmyelinated sensory and sympathetic fibers, which exhibit greater sensitivity to local anesthetics, whereas the ventral roots comprise myelinated motor fibers that are less sensitive [20].

The sequence in which local anesthetics block various nerve fibers is as follows: autonomic nerves are affected first, followed by sensory fibers, then motor fibers, and finally myelinated proprioceptive fibers. The order of block onset is: vasomotor fibers → cold sensation → warmth sensation → temperature discrimination → slow pain → fast pain → touch sensation → motor paralysis → pressure sensation → proprioception. Recovery from anesthesia follows the reverse sequence [38].

Notably, sympathetic blockade always precedes sensory blockade and lasts the longest, which can lead to postoperative hypotension and orthostatic hypotension. Therefore, it is crucial to avoid premature positional changes after surgery. The levels of sympathetic, sensory, and motor blocks do not correspond uniformly. Typically, the sympathetic block is two to four segments higher than the sensory block, and the sensory block is one to four segments higher than the motor block. This disparity is essential for clinicians to consider when managing patients under intrathecal anesthesia, as it influences both the efficacy and safety of the anesthetic technique [6, 39].

Understanding the differential sensitivity of nerve fibers to local anesthetics is vital in optimizing the dosage and administration of intrathecal anesthetics. For instance, the higher sensitivity of unmyelinated fibers necessitates precise dosing to avoid adverse effects while ensuring adequate anesthesia. The clinical implications of these findings include better management of patient positioning, monitoring, and postoperative care to mitigate risks such as hypotension and to ensure effective pain relief and motor function recovery [40].

7.4.2 Epidural Anesthesia

Epidural anesthesia involves administering local anesthetics into the epidural space, where these agents diffuse both vertically and into the surrounding tissues. This method can provide anesthesia for a variety of surgical procedures and pain relief, especially during childbirth [41].

Some anesthetics may produce paravertebral nerve blocks, while others may cross into the subarachnoid space, thereby affecting spinal nerve roots and

peripheral nerves [36]. Additionally, local anesthetics can permeate the dura and arachnoid membranes, entering the cerebrospinal fluid, which can result in delayed-onset spinal anesthesia.

Unlike subarachnoid anesthesia, epidural anesthesia necessitates larger volumes of anesthetics due to the need for extensive diffusion to achieve the desired block. The volume of anesthetic used is crucial in determining the extent of the block, while the concentration of the anesthetic influences the quality of the block. Higher concentrations are associated with more complete blocks of motor, sensory, and autonomic functions. Conversely, diluting the anesthetic can produce differential blocks, which are beneficial for postoperative analgesia by selectively blocking sensory nerves while preserving motor function [42].

Epidural anesthesia can be administered at various spinal levels, with the level and degree of the block being adjusted by modifying the volume and concentration of the anesthetic. This flexibility makes epidural anesthesia a versatile tool for pain management in different clinical settings [6].

7.4.3 Local Anesthetics

Local anesthetics are used to numb specific areas of the body for minor surgical procedures, dental work, and diagnostic tests. These agents rarely have direct effects on the cerebral cortex; instead, they primarily enter the brain through the bloodstream.

The effects of local anesthetics on the central nervous system are concentration-dependent. Low concentrations, such as those of procaine, can provide inhibitory, analgesic, and anticonvulsant effects. However, at higher concentrations, these agents can induce seizures. Local anesthetics like lidocaine, mepivacaine, dibucaine, and even cocaine possess anticonvulsant properties, with lidocaine having a particularly wide therapeutic range [43].

The anticonvulsant dose of lidocaine is close to its therapeutic dose for treating arrhythmias, which ranges from 1 to 5 μg/ml. Seizures induced by local anesthetics are an indication of toxicity. A sudden increase in the blood concentration of local anesthetics can lead to a spectrum of toxic symptoms, which progress in severity from tongue or lip numbness, headache, dizziness, and tinnitus to more serious manifestations like blurred vision, difficulty focusing, nystagmus, slurred speech, muscle twitching, incoherent speech, confusion, seizures, coma, and respiratory arrest [44].

Blood concentrations typically range from 4 to 6 μg/ml for most local anesthetics, but potent agents like bupivacaine or etidocaine can cause toxicity at lower concentrations (around 2 μg/ml). Toxic symptoms can present even in the absence of significant EEG changes. EEG manifestations of amide local anesthetic toxicity include the loss of alpha waves and increased slow theta and delta waves [45]. Seizures caused by local anesthetics are generalized tonic-clonic seizures, characterized by muscle spasms that can impede respiration.

High blood levels of local anesthetics depress cardiovascular function, leading to reduced cerebral blood flow and oxygenation, which indirectly affects brain

function. These seizures may involve parts of the brain such as the limbic system, hippocampus, and amygdala—the latter of which has a richer blood supply, facilitating easier penetration by local anesthetics. Local anesthetics selectively inhibit cortical inhibitory pathways, resulting in unopposed neuronal discharge and subsequent excitement and seizures. Further increases in blood concentration can inhibit both excitatory and inhibitory pathways, leading to a broad suppression of the central nervous system [46].

7.5 Anesthetic Adjuncts

7.5.1 Dexmedetomidine

Dexmedetomidine is a highly selective α2-adrenoceptor agonist, renowned for its 1620:1 selectivity ratio for α2 over α1 receptors. This selectivity ensures it maintains hemodynamic stability by promoting vasodilation and lowering sympathetic outflow, leading to controlled decreases in heart rate and blood pressure without severe hypertension or reflex tachycardia. Its action on both central and peripheral α2 receptors provides a combination of sedation, analgesia, and reduced sympathetic activity without significant respiratory depression [47].

The primary central site of action for dexmedetomidine is the locus coeruleus, an area in the brainstem densely populated with α2 receptors critical for regulating arousal. Activation of these receptors produces sedation similar to natural sleep, easily reversible with verbal stimuli. This makes dexmedetomidine particularly useful in neurosurgical procedures where patient cooperation is necessary for tasks such as neural localization and lesion removal.

- **Sedation and Anxiolysis**
  Dexmedetomidine is highly effective for preoperative sedation, significantly reducing preoperative anxiety, which can otherwise lead to adverse reactions. As a premedication, it provides effective sedation, alleviating anxiety and diminishing stress responses before surgery [48]. For instance, in neurosurgical settings, its sedative effects can facilitate patient cooperation without compromising respiratory function. A notable case reported by Plunkett and colleagues involved a patient with severe cardiopulmonary disease who successfully underwent thyroid surgery under regional anesthesia with a continuous infusion of dexmedetomidine. The patient maintained adequate cooperation with the surgical team, highlighting dexmedetomidine's efficacy in complex clinical scenarios [49].
- **Pain Management**
  Dexmedetomidine plays a crucial role in pain management by inhibiting the release of norepinephrine from presynaptic and spinal α2 receptors, blocking pain signal transmission and providing analgesia. Research by Mizrak et al. demonstrated that a continuous infusion of dexmedetomidine at 0.5 μg/kg before local anesthesia enhanced both the quality of anesthesia and the analgesic effect. Similarly, Mohamed et al. found that adding 1 μg/kg of dexmedetomidine to

0.25% bupivacaine in thoracic epidural anesthesia during modified radical mastectomy resulted in superior analgesia, prolonged pain relief, and reduced postoperative analgesic needs.

- **Cardiovascular Stability**
  Dexmedetomidine also offers cardiovascular stability by reducing heart rate and blood pressure, making it a valuable adjunct in patients with cardiovascular concerns. Its ability to maintain hemodynamic stability without significant respiratory depression makes it an ideal choice for various surgical settings, including those involving high-risk patients [48].
- **Neuroprotective Effects**
  Dexmedetomidine's neuroprotective effects have garnered significant interest. Studies suggest it can mitigate ischemic neuronal injury by reducing excitotoxicity and oxidative stress, thereby protecting the brain during surgeries that risk cerebral ischemia. This neuroprotection adds another layer of benefit, particularly in neurosurgical and high-risk cardiovascular procedures [50].

Dexmedetomidine's combination of sedative, analgesic, and anxiolytic properties, along with its ability to maintain cardiovascular stability and offer neuroprotection, makes it an invaluable adjunct in anesthesia. Its unique pharmacological profile allows for a wide range of applications, from managing preoperative anxiety to providing intraoperative sedation and analgesia, especially in high-risk patients. The growing body of evidence supporting its efficacy and safety continues to solidify its role in modern anesthetic practice [20].

7.5.2 Benzodiazepines

Benzodiazepines primarily exert their effects by acting on the brainstem reticular formation and limbic structures, including the amygdala and hippocampus. These brain regions play crucial roles in regulating emotional responses. Noradrenergic neurons, which increase anxiety, and serotonergic neurons, which inhibit anxiety, interact to maintain emotional balance. Benzodiazepines enhance the action of the inhibitory neurotransmitter GABA and increase serotonin levels in the brain. By inhibiting noradrenergic neurons, GABA reduces anxiety [51].

In 1977, independent research teams led by Squires and Braestrup in Denmark [52] and Möhler and Okada in Switzerland [53] identified benzodiazepine (BZ) receptors in animal brains, a finding that was later confirmed in humans. BZ receptors are widely distributed throughout the central nervous system and in various peripheral tissues. The highest densities of these receptors are found in the frontal and occipital cortex, hippocampus, and cerebellar cortex, with moderate densities in the striatum, globus pallidus, hypothalamus, and lower densities in the medulla and spinal cord.

BZ receptors are located on the synaptic membranes of neurons, closely associated with GABA receptors, forming part of the GABA receptor-chloride ion channel complex. The regulatory protein GABA-modulin inhibits GABA binding to its

receptor. Benzodiazepines bind to BZ receptors, blocking the action of GABA-modulin, which enhances GABA binding to its receptor. This promotes the opening of chloride channels, leading to neuronal hyperpolarization and the various pharmacological effects of benzodiazepines [54]. The anxiolytic effects are believed to result from binding to receptors in the limbic system, while anticonvulsant effects are associated with cortical receptors, and muscle relaxant effects are linked to spinal cord receptors [55].

The pharmacological effects of benzodiazepines are dose-dependent and correlate with BZ receptor occupancy. Studies have shown that approximately 20% receptor occupancy is needed to produce anxiolytic effects, 30–50% occupancy results in sedation, and greater than 60% occupancy induces hypnotic effects.

Benzodiazepines also have significant effects on cerebral blood flow and metabolism. Research indicates that diazepam can reduce both cerebral blood flow and metabolism in patients with brain injuries. When used in conjunction with 70% nitrous oxide anesthesia, diazepam or midazolam can reduce cerebral blood flow by up to 45% even before changes in oxygen metabolism occur. Increasing doses of midazolam result in a proportional reduction in cerebral blood flow and metabolism. Clinically, administering midazolam at a dose of 0.15 mg/kg can reduce cerebral blood flow by 33% and slightly increase carbon dioxide sensitivity [56].

Benzodiazepines can be safely administered to patients with elevated intracranial pressure, provided that carbon dioxide levels are adequately controlled. This makes them a valuable option in managing anxiety and agitation in such patients, without significantly compromising cerebral perfusion [57].

7.5.3 Chlorpromazine

Chlorpromazine is a potent central nervous system (CNS) depressant that exerts its effects primarily on the limbic system, reticular formation, and hypothalamus. It induces a state of tranquility, reduces motor activity, fosters apathy, and causes drowsiness, with EEG patterns that resemble natural sleep. Additionally, chlorpromazine enhances the effects of other CNS depressants, including hypnotics and analgesics [58, 59].

A key feature of chlorpromazine is its ability to inhibit the hypothalamus, leading to autonomic blockade. This produces significant antiadrenergic effects and mild anticholinergic effects, contributing to its anti-shock properties [60]. This drug also influences the thermoregulatory center, impairing the body's response to cold and facilitating heat loss, making it useful for managing hyperthermia.

Chlorpromazine also has recognized for its strong antiemetic properties, achieved through the suppression of the chemoreceptor trigger zone in the fourth ventricle, making it highly effective in preventing nausea and vomiting.

However, prolonged use of high doses can lead to extrapyramidal side effects such as tremors, increased muscle tone, bradykinesia, and akathisia. These symptoms typically resolve after discontinuation of the drug. In more severe cases, anticholinergic medications may be administered to alleviate these effects. Another

serious, though rare, complication of long-term use of chlorpromazine is neuroleptic malignant syndrome, which requires prompt medical attention [61].

The broad range of effects make chlorpromazine a versatile agent in anesthesia and critical care. Its tranquilizing properties and ability to enhance other anesthetics make it valuable in preoperative preparation. Its autonomic blockade function is beneficial in managing shock, while its antiemetic properties are crucial in preventing postoperative nausea and vomiting [62, 63].

7.5.4 Haloperidol

Haloperidol, a potent antipsychotic, exerts its therapeutic effects for up to 24 h but has less pronounced sedative properties compared to chlorpromazine. Its antiadrenergic activity is also milder, resulting in minimal impact on blood pressure. Notably, haloperidol has significant antiemetic capabilities, approximately 50 times more potent than chlorpromazine, and it augments the effects of barbiturates and analgesics without markedly affecting respiration [64].

Haloperidol is widely recognized for its strong antipsychotic effects, making it valuable in managing acute and chronic psychotic disorders. Despite its robust antipsychotic action, its sedative effects are relatively weak, which can be advantageous in situations where sedation is not desirable. Its antiemetic properties are particularly beneficial in preventing and treating nausea and vomiting, especially in patients undergoing chemotherapy or surgery [65].

One of the key benefits of haloperidol is its ability to enhance the efficacy of barbiturates and analgesics. This synergistic effect allows for lower dosages of these medications, reducing their potential side effects while maintaining therapeutic efficacy. Importantly, haloperidol does not significantly depress respiratory function, which is a critical consideration in perioperative and critical care settings.

A common side effect of haloperidol is the occurrence of extrapyramidal symptoms, including movement disorders such as dystonia, parkinsonism, and akathisia. These reactions are due to its potent dopamine receptor antagonism in the central nervous system. A severe but rare adverse effect of haloperidol is neuroleptic malignant syndrome (NMS), characterized by hyperthermia, increased muscle rigidity, altered mental status, and autonomic instability. NMS is associated with elevated transaminase and creatine phosphokinase levels and has a mortality rate of up to 20%. The pathophysiology of NMS is believed to involve excessive central dopamine receptor blockade, leading to dopaminergic dysfunction [66, 67]. Monitoring and managing these side effects are crucial for patients on long-term haloperidol therapy [68].

Animal studies have shown that combining haloperidol with nitrous oxide anesthesia can reduce cerebral blood flow by 40% without significantly altering oxygen metabolism and cerebral metabolic rate. Clinically, the combination of haloperidol and fentanyl anesthesia does not substantially affect cerebral blood flow and metabolism. Adding haloperidol or fentanyl to nitrous oxide anesthesia has been observed to slightly decrease intracranial pressure without compromising cerebral perfusion

pressure. In neurosurgical patients, haloperidol or fentanyl does not significantly reduce intracranial pressure compared to thiopental. This makes haloperidol a useful adjunct in neurosurgery where managing intracranial pressure is crucial. Furthermore, preoperative administration of haloperidol at doses ranging from 2.5 to 7.5 mg does not affect EEG readings, indicating its safety in maintaining neural activity stability during surgery [69].

7.5.5 Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are powerful nonselective monoamine reuptake inhibitors that primarily target the reuptake of norepinephrine (NA) and serotonin (5-HT). By inhibiting the reabsorption of these neurotransmitters, TCAs increase their concentrations in the synaptic cleft, leading to enhanced neurotransmission and improved mood in depressive disorders. This mechanism is shared by some other antidepressants, such as venlafaxine [70].

The primary therapeutic action of TCAs is the inhibition of norepinephrine and serotonin reuptake. This increase in neurotransmitter levels in the synaptic cleft contributes to their antidepressant efficacy. Enhanced levels of norepinephrine and serotonin improve synaptic transmission, which is crucial for mood regulation.

TCAs exhibit significant anticholinergic properties, leading to side effects such as dry mouth, constipation, and urinary retention [71]. Additionally, they block α1-adrenergic and H1 histamine receptors, contributing to sedation and orthostatic hypotension. These anticholinergic effects can cause blurred vision and dizziness, which may impair cognitive functions such as attention and thinking, especially in the early stages of treatment [72].

In individuals without depression, TCAs often induce feelings of calmness and drowsiness. The initial reduction in blood pressure and other side effects, such as dizziness and blurred vision, are attributed to their anticholinergic activity. These effects may become more pronounced with prolonged use, potentially leading to cognitive impairment. For patients suffering from depression, the therapeutic benefits of TCAs are more pronounced. After 2–3 weeks of continuous use, patients typically experience an increase in energy levels and significant mood improvements. This delayed onset of antidepressant effects is due to the time required for neurotransmitter levels to stabilize and for the brain to adapt to the increased synaptic activity [73].

TCAs can be combined with other therapeutic strategies to enhance their efficacy and mitigate side effects. For instance, the concurrent use of selective serotonin reuptake inhibitors (SSRIs) can provide a more balanced neurotransmitter modulation, reducing the risk of severe anticholinergic effects [74]. Additionally, incorporating non-pharmacological treatments such as cognitive-behavioral therapy (CBT) can offer a comprehensive approach to managing depression [75].

To optimize the therapeutic outcomes of TCAs, careful monitoring of side effects is essential. Adjusting dosages and employing supportive treatments can help manage anticholinergic effects and minimize cognitive impairments. Regular

follow-ups and patient education on potential side effects can enhance adherence to treatment and improve overall patient outcomes.

7.5.6 Selective Serotonin Reuptake Inhibitors Introduction

Selective serotonin reuptake inhibitors (SSRIs) represent a class of modern antidepressants that target the serotonin (5-HT) system with high specificity. Unlike older antidepressants, SSRIs primarily inhibit the reuptake of serotonin without significantly impacting norepinephrine (NE) or dopamine (DA) reuptake. This selectivity makes SSRIs effective and generally well tolerated in the treatment of depression and anxiety disorders [76].

SSRIs exert their therapeutic effects by selectively blocking the reuptake of serotonin into the presynaptic neuron. This action increases the availability of serotonin in the synaptic cleft, enhancing serotonergic neurotransmission. The increased serotonin levels help alleviate symptoms of depression and anxiety by improving mood and emotional regulation [77].

SSRIs are widely used for the treatment of major depressive disorder and various anxiety disorders, including generalized anxiety disorder, panic disorder, and social anxiety disorder. Their ability to enhance serotonergic activity in the brain makes them effective in reducing depressive symptoms and anxiety. Compared to older classes of antidepressants, such as TCAs and monoamine oxidase inhibitors (MAOIs), SSRIs have a more favorable side effect profile. They are less likely to cause sedation, weight gain, and cardiovascular side effects, making them a preferred choice for many patients [78].

Although SSRIs are generally well tolerated, they can cause a range of side effects, including gastrointestinal disturbances (nausea, diarrhea), sexual dysfunction, and insomnia. These side effects are usually mild and often diminish with continued use. One significant risk associated with SSRIs is serotonin syndrome, a condition characterized by excessive accumulation of serotonin in the brain. Symptoms include agitation, confusion, rapid heart rate, and high blood pressure. This syndrome can occur when SSRIs are combined with other serotonergic drugs, necessitating careful management and awareness by healthcare providers [79].

Effective use of SSRIs requires regular patient monitoring to adjust dosages and manage side effects. Educating patients about the potential side effects and the importance of adherence to prescribed regimens can improve treatment outcomes and reduce the risk of complications [80].

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Advanced Central Nervous System Monitoring in Anesthesia Practice

8

The central nervous system (CNS) serves as the control center for all physiological and cognitive processes in the human body. Monitoring its function is crucial for diagnosing, treating, and managing various neurological conditions, ranging from traumatic brain injuries and strokes to epilepsy and neurodegenerative disorders. Advances in technology have enabled the development of sophisticated CNS monitoring techniques that provide real-time data on brain and spinal cord activity, metabolism, hemodynamics, and structural integrity. These techniques are indispensable in critical care, surgical settings, and research, allowing for early detection of abnormalities, precise interventions, and improved patient outcomes. This chapter explores the principles, applications, and recent innovations in CNS monitoring, highlighting their role in advancing neurological care.

8.1 Electroencephalography (EEG)

Electroencephalography (EEG) is a noninvasive technique used to record the brain's spontaneous rhythmic electrical activity. It provides valuable insights into brain function and is widely employed in both clinical and research settings. The International Federation of Clinical Neurophysiology (IFCN) endorses the International 10–20 system for electrode placement. This system ensures that electrodes are proportionally placed according to the size and shape of the patient's head, with each electrode corresponding to specific anatomical regions of the brain. The standard configuration involves 21 electrodes, but this can be adjusted based on the specific requirements of the examination [1].

EEG recordings are performed in a controlled environment, typically a quiet room with a comfortable temperature to minimize external influences on the patient's state. Patients are usually instructed to be in a relaxed state, either awake or asleep, with their eyes closed. This setup helps to obtain a clear baseline of the brain's electrical activity. Additionally, various induced tests, such as hyperventilation, photic stimulation, or sleep deprivation, can be employed to enhance the

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diagnostic yield of the EEG, revealing abnormalities that might not be apparent under resting conditions.

In healthy adults, the dominant rhythm observed when awake, relaxed, and with eyes closed is the alpha rhythm. This rhythm has a frequency range of 7.5–12 Hz and an amplitude of 20–100 μV, predominantly seen in the occipital and parietal regions. Beta activity, which has a frequency range of 12–30 Hz and an amplitude of 5–20 μV, is mainly detected in the frontal and temporal lobes. While theta waves (4–7.5 Hz) are typically more common in the anterior brain regions of normal individuals, they are less prevalent in adults. Delta waves (less than 4 Hz) are generally associated with sleep and are not typically present during wakefulness**.**

In children, the EEG patterns differ significantly from those of adults. Younger children exhibit a predominance of slow wave activity, which gradually decreases as they age. By the time they reach adolescence (around 14–18 years), their EEG patterns closely resemble those of adults, with a notable increase in alpha wave activity. Understanding these age-related changes is crucial for accurately interpreting EEG results in pediatric populations [2].

EEG is a critical tool in the diagnosis and monitoring of various neurological conditions. It is widely used to evaluate epilepsy, sleep disorders, encephalopathies, and other brain dysfunctions. By analyzing the electrical patterns of the brain, clinicians can identify abnormal activities such as epileptic spikes or unusual slowing, which are indicative of underlying neurological issues [3]. Furthermore, EEG is essential in the intraoperative monitoring of brain function during surgeries that pose a risk to the central nervous system, helping to prevent potential damage and guide surgical interventions [4].

To improve the accuracy and reliability of EEG interpretations, advanced techniques such as quantitative EEG (qEEG) are employed. qEEG involves the mathematical analysis of EEG data, providing a more detailed and objective assessment of brain function. This technique can identify subtle abnormalities and trends that might be missed in standard EEG recordings [5]. Additionally, combining EEG with other neuroimaging modalities, such as magnetic resonance imaging (MRI) or positron emission tomography (PET), can offer a more comprehensive view of brain activity and structure [6].

8.2 Monitoring of Evoked Potential

Evoked potentials (EPs) are electrical responses generated by the nervous system following specific sensory, motor, or cognitive stimuli. These potentials are crucial in assessing the functional integrity of various neural pathways. Due to their typically low amplitude (ranging from 0.1 to 20 μV), EPs are often masked by the brain's spontaneous electrical activity (25–80 μV) and other artifacts. To extract meaningful data, averaging and superimposition techniques are employed to enhance the signal-to-noise ratio, making the evoked activity discernible [7].

Types of Evoked Potentials

- **Somatosensory Evoked Potentials (SSEPs)**
  SSEPs assess the functional status of the somatosensory pathways from peripheral nerves through the spinal cord to the cerebral cortex. They are elicited by electrical stimulation of peripheral nerves, such as the median or tibial nerves, and are crucial for monitoring during surgeries that risk damage to the spinal cord or peripheral nerves [8].
- **Visual Evoked Potentials (VEPs)**
  VEPs evaluate the visual pathways from the retina to the visual cortex. These potentials are generated by visual stimuli, such as flashing lights or pattern reversals. VEPs are particularly useful in diagnosing and monitoring conditions like optic neuritis, multiple sclerosis, and other disorders affecting the visual pathways [8].
- **Auditory Evoked Potentials (AEPs)**
  AEPs measure the integrity of the auditory pathways from the cochlea through the brainstem to the auditory cortex. They are elicited by auditory stimuli, such as clicks or tones, and are vital for assessing hearing in newborns and diagnosing auditory pathway disorders [8].
- **Motor Evoked Potentials (MEPs)**
  MEPs assess the functional integrity of the motor pathways from the motor cortex to the muscles. They are elicited by transcranial magnetic or electrical stimulation of the motor cortex and are essential for intraoperative monitoring during surgeries that pose a risk to motor pathways [9].

EP monitoring is integral in various clinical settings, including diagnosing neurological disorders, monitoring disease progression, and guiding surgical procedures. Intraoperative monitoring of EPs is particularly valuable in spinal and brain surgeries, where real-time feedback on neural pathway integrity can prevent permanent damage and improve surgical outcomes [10].

The recording of EPs requires precise electrode placement and careful control of external variables to minimize artifacts. Techniques such as signal averaging, which involves repeating the stimulus multiple times and averaging the responses, help in isolating the evoked response from background noise. Additionally, advanced filtering techniques are employed to further enhance the clarity of the evoked potentials. Recent advancements in EP technology include the development of more sophisticated signal processing algorithms and portable monitoring devices, making EP monitoring more accessible and accurate. The integration of EPs with other neuroimaging modalities, such as functional MRI (fMRI) and magnetoencephalography (MEG), offers a comprehensive view of brain activity and connectivity, enhancing diagnostic accuracy and treatment planning [7].

8.3 Monitoring of Intracranial Pressure

The cranial cavity has limited tolerance for volume changes, and under normal conditions, brain tissue, blood, and cerebrospinal fluid (CSF) volumes are in equilibrium within the cranial and spinal compartments. The Monro-Kellie doctrine elucidates this relationship, stating that any increase in one component requires a compensatory decrease in another to maintain stable intracranial pressure (ICP) [11, 12]. When these compensatory mechanisms fail, even minimal increases in volume can lead to rapid and exponential rises in ICP. Elevated ICP can decrease cerebral perfusion pressure (CPP = MAP – ICP, where MAP is mean arterial pressure), leading to cerebral ischemia. Severe increases in ICP can result in brain herniation, causing fatal ischemia of brain tissue or the brainstem [13]. Intracranial pressure monitoring is crucial in managing patients with conditions that predispose them to elevated ICP. The intraventricular catheter (IVC), also known as an external ventricular drain (EVD), is considered the "gold standard" for ICP monitoring. This device measures pressure by transmitting it from the CSF-filled ventricles through a fluid-filled catheter to an external transducer. Accurate ICP measurement relies on free communication between all CSF compartments [14].

The IVC is typically inserted into the anterior horn of the lateral ventricle through a burr hole at Kocher's point. Ideally, the catheter tip should be placed in the ventricle opposite the lesion causing mass effect. However, if there is significant midline shift and obliteration of the contralateral ventricle, the catheter should be placed in the ipsilateral ventricle to avoid worsening the shift. The sensor system of the IVC is calibrated to zero at the foramen of Monro, level with the external auditory meatus. Unlike some parenchymal monitoring devices, the IVC can be recalibrated after insertion, enhancing its reliability [15].

One of the significant advantages of the IVC is its diagnostic and therapeutic utility. Besides monitoring ICP, the IVC allows for CSF drainage to manage acute increases in pressure. This capability is vital in neurocritical care settings, where rapid intervention can prevent severe outcomes. Additionally, the IVC can be used for administering medications directly into the CSF, such as antibiotics or thrombolytics, and for sampling CSF for laboratory analysis [16, 17].

The use of IVCs in managing intracranial pressure exemplifies the intersection of diagnostic and therapeutic approaches in neurocritical care. By facilitating accurate monitoring and enabling direct intervention, IVCs play a pivotal role in improving patient outcomes in conditions associated with elevated ICP [18].

8.4 Monitoring of Cerebral Blood Flow

8.4.1 ^{133}Xe Clearance Method

The ^{133}Xe clearance method utilizes the soluble, inert gas xenon-133, which rapidly diffuses from the bloodstream into brain tissue and is subsequently cleared. Gamma-ray detectors are employed to measure the cerebral clearance of the isotope,

providing two-dimensional imaging data. This method, widely used in intensive care unit (ICU) settings, has certain theoretical limitations due to its two-dimensional imaging, which can lead to inaccuracies, particularly in low-flow states. Additionally, maintaining a stable partial pressure of ^{133}Xe presents a significant challenge. Despite advancements in multi-detector technology, achieving precise anatomical localization remains difficult, rendering this technique more suitable for monitoring diffuse brain pathologies rather than localized issues [19].

8.4.2 Positron Emission Tomography (PET)

Positron emission tomography (PET) is an advanced imaging technique that detects high-energy photons emitted from positron-electron interactions. Utilizing a cyclotron and PET scanner, this method generates a series of cross-sectional images of the brain, offering detailed insights into cerebral blood flow, blood volume, metabolic activity, and the functionality of deep brain structures. Commonly used radioisotopes include $^{15}O_2$-labeled CO_2, ^{18}F, ^{11}C, and ^{13}N. PET provides valuable pathophysiological data, although its use in routine clinical monitoring is limited due to its complexity and cost [19].

8.4.3 Impedance Method

Impedance plethysmography measures cerebral blood flow based on the principle that blood has the lowest electrical impedance among all tissues. This technique reflects changes in cerebral blood volume but is influenced by numerous factors, limiting its clinical utility. While it can provide insights into cerebral hemodynamics, the method's susceptibility to external variables hinders its widespread application in routine clinical practice [20, 21].

8.4.4 Transcranial Doppler (TCD)

Transcranial Doppler (TCD) employs Doppler ultrasound technology to emit low-frequency sound waves capable of penetrating the cranial bones and obtaining signals from basal cerebral arteries. TCD provides noninvasive, continuous, and dynamic monitoring of cerebral hemodynamics, most commonly measuring the flow velocity in the middle cerebral artery. This flow velocity is a reliable indicator of cerebral blood flow changes, making TCD a valuable tool for real-time monitoring of cerebral circulation and detecting conditions such as vasospasm, emboli, and autoregulatory function [22].

8.4.5 Near-Infrared Spectroscopy (NIRS)

Near-infrared spectroscopy (NIRS) is a technique that involves the injection of an infrared tracer through a central venous catheter into the right atrium. As the tracer circulates through the cerebral vasculature, changes in the recorded signal are analyzed to calculate cerebral transit time, which is indicative of cerebral blood flow. The mean transit time, defined as the ratio of cerebral blood volume to cerebral blood flow, provides valuable information on cerebral perfusion and oxygenation, particularly useful in neonatal and pediatric intensive care settings [20, 23].

8.4.6 Laser Doppler Flowmetry

Laser Doppler flowmetry uses a helium-neon laser to illuminate the brain cortex. By analyzing the Doppler shift in the reflected light, this technique measures local cortical blood perfusion and tracks perfusion trends over time. Laser Doppler flowmetry offers a noninvasive, continuous means of monitoring cerebral microcirculation, making it particularly useful for assessing cerebral autoregulation and CO_2 reactivity. Its ability to provide real-time data on local blood flow dynamics enhances its utility in both research and clinical settings [24, 25].

In conclusion, various techniques for monitoring cerebral blood flow each offer unique advantages and limitations. The choice of method depends on the clinical context, the need for precision, and the specific information required for patient management. Combining multiple monitoring techniques can provide a more comprehensive assessment of cerebral hemodynamics, ultimately improving patient outcomes in critical care and neurosurgical environments.

8.5 Monitoring of Brain Metabolism

Monitoring cerebral metabolism is essential for assessing brain function, particularly in critical care and surgical settings. Key parameters include the cerebral metabolic rate for oxygen ($CMRO_2$) and glucose (CMRglu), which require precise measurements of cerebral blood flow (CBF), arterial oxygen content (CaO_2), arteriovenous difference of oxygen ($avDO_2$), and jugular venous oxygen content (CjO_2). The formula for $CMRO_2$ is: $CMRO_2 = CBF \times (CaO_2 - CjO_2)$ [26]. Similarly, CMRglu is calculated by measuring glucose uptake and utilization within the brain. This method is frequently used in animal studies but is less common clinically due to the challenges associated with using radioactive isotopes [27]. Clinically, an estimated $CMRO_2$ ($eCMRO_2$) is often used as a proxy: $eCMRO_2 = avDO_2 \times PaCO_2 \times (CBF/PaCO_2)/100$. Several primary techniques for monitoring cerebral metabolism include jugular venous oxygen saturation ($SjvO_2$), near-infrared spectroscopy (NIRS), brain tissue oxygen tension ($PbtO_2$), and magnetic resonance spectroscopy (MRS) [28].

8.5.1 Jugular Venous Oxygen Saturation Monitoring

Jugular venous oxygen saturation ($SjvO_2$) provides an indirect measure of the balance between cerebral oxygen supply and demand. This technique involves retrograde catheter placement in the jugular vein to measure hemoglobin oxygen saturation just above the jugular bulb. Normal $SjvO_2$ values range from 55% to 71%, reflecting adequate cerebral perfusion. Values below 50% indicate potential cerebral ischemia or hypoxia, while elevated $SjvO_2$ may suggest conditions such as cerebral hyperemia, reduced metabolic rate, or brain death, indicating decreased oxygen utilization and increased arteriovenous shunting [26].

8.5.2 Near-Infrared Spectroscopy (NIRS) Monitoring

Near-infrared spectroscopy (NIRS) uses light in the 650–1100 nm range to penetrate brain tissue, measuring cerebral oxygenation based on the absorption characteristics of oxyhemoglobin, deoxyhemoglobin, and cytochromes. The difference between incident and reflected light intensities is used to calculate regional cerebral oxygen saturation (rSO_2), primarily reflecting venous blood oxygenation. Normal rSO_2 values are around 64% ± 3.4%; values below 55% suggest potential abnormalities. Factors affecting rSO_2 include hypoxia, increased intracranial pressure (ICP), and reduced cerebral perfusion pressure. NIRS is particularly useful for intraoperative monitoring in complex neurosurgical and cardiac procedures, providing real-time data on brain metabolism and prognostic indicators [26, 29].

8.5.3 Brain Tissue Oxygen Tension Monitoring

Brain tissue oxygen tension ($PbtO_2$) monitoring involves the use of a local probe to directly measure the oxygen level within brain tissue, offering an invasive but highly accurate assessment of cerebral oxygenation status. The normal $PbtO_2$ range is 16–40 mmHg, with values between 10 mmHg and 15 mmHg indicating mild hypoxia and values below 10 mmHg indicating severe hypoxia. $PbtO_2$ monitoring is predominantly used in cases of severe traumatic brain injury, guiding therapeutic interventions and helping to predict outcomes [30].

8.5.4 Magnetic Resonance Spectroscopy (MRS)

Magnetic resonance spectroscopy (MRS) provides a noninvasive method for assessing brain metabolism by detecting chemical shift effects, which are slight changes in the magnetic field surrounding nuclei in different chemical environments. MRS measures these shifts in parts per million (ppm), relative to a specific reference substance, providing insights into various metabolic products that reflect neural integrity, energy metabolism, and membrane turnover. This technique is valuable for

identifying metabolic abnormalities in various neurological conditions, including brain tumors, epilepsy, and neurodegenerative diseases [273].

8.6 Monitoring of Spinal Cord Function

Monitoring spinal cord function is critical during surgeries involving the spinal column or spinal cord to ensure neural integrity and prevent postoperative deficits. The main techniques include intraoperative spinal cord evoked potentials and transcranial electrical or magnetic stimulation evoked potentials [31].

8.6.1 Intraoperative Spinal Cord Evoked Potentials

Peripheral nerve stimulation can elicit evoked potentials in the spinal cord, providing real-time monitoring of spinal cord integrity. This method involves placing catheter electrodes near the cervical or lumbar enlargement in the epidural space. For cervical spinal cord monitoring, the electrodes are positioned near the cervical enlargement, and stimulation is applied to the brachial, radial, ulnar, or median nerve. This setup monitors the function of the cervical spinal cord segments. Similarly, for lumbar spinal cord monitoring, electrodes are placed near the lumbar enlargement, and the tibial or common peroneal nerve is stimulated [32].

8.6.2 Intraoperative Transcranial Electrical or Magnetic Stimulation Evoked Potentials

Transcranial stimulation techniques are used to assess the functional integrity of the corticospinal tract. Transcranial electrical stimulation (TES) involves placing electrodes on the scalp at positions C3 and C4 and delivering a series of square wave pulses (250–1000 V) at intervals of 0.2 ms, with pulse durations ranging from 0.02 to 0.2 ms. Due to the high voltage, durable electrodes such as corkscrew electrodes are required to prevent local skin burns.

Transcranial magnetic stimulation (TMS) uses an electromagnetic coil to generate a magnetic field, inducing electrical currents in the brain. This method is less invasive and can reduce patient discomfort. Evoked potentials are recorded using electromyography (EMG) with needle electrodes placed in muscles such as the abductor pollicis brevis for the upper limbs or the tibialis anterior for the lower limbs [33].

During TES, large pyramidal cells in the motor cortex are directly depolarized, producing direct (D) waves. TMS initially depolarizes interneurons, which then depolarize pyramidal cells, generating indirect (I) waves approximately 1.5–2.0 ms later. The combination of D and I waves forms complex spikes that travel down the corticospinal tract, ultimately stimulating spinal motor neurons and producing excitatory postsynaptic potentials (EPSPs). This spinal motor neuron excitation has

a delay of several milliseconds. While awake patients may experience seizures during stimulation, such occurrences are rare under general anesthesia. Monitoring is essential during spinal surgeries to ensure spinal cord integrity and prevent neurological damage [34, 35].

8.6.3 Intraoperative Transcranial Stimulation Spinal Cord Evoked Potentials Monitoring

Transcranial stimulation can also be used to monitor spinal cord potentials, which can provide superior information about spinal cord function compared to motor evoked potentials (MEPs) alone. This technique involves altering spinal cord potentials through transcranial electrical or magnetic stimulation. The methods for transcranial electrical and magnetic stimulation, as well as the recording techniques for transcranial stimulated evoked spinal cord potentials (tc-SCPs), are similar to those used for monitoring segmental spinal cord evoked potentials [31, 36].

8.7 Central Nervous System Imaging

Imaging techniques play a critical role in diagnosing, prognosticating, and understanding the pathophysiology of neurological disorders. These techniques can be broadly categorized into anatomical (structural) and functional (physiological) imaging. Structural imaging methods like computed tomography (CT) and magnetic resonance imaging (MRI) provide detailed visuals of cranial structures, brain parenchyma, central nervous system (CNS) vasculature, cerebrospinal fluid (CSF), the spine, the spinal cord, and spinal nerves. They are invaluable for identifying intracranial hemorrhage, tumors, aneurysms, and vascular malformations. Functional imaging techniques, including perfusion CT (PCT), diffusion-weighted MRI (DWI), diffusion tensor imaging (DTI), perfusion-weighted MRI (PWI), and magnetic resonance spectroscopy (MRS), offer insights into the physiological and biological aspects of brain function [37].

8.7.1 Plain X-Ray

Despite advancements in CT and MRI, plain X-rays remain useful, particularly in cases of brain trauma. They are effective in detecting skull and spinal fractures and are commonly used to screen for metal objects before an MRI scan. However, they are less sensitive than CT for detailed intracranial and intraspinal evaluations and cannot accurately assess soft tissue injuries or vascular abnormalities [38, 39].

8.7.2 Computed Tomography (CT)

CT is the preferred initial imaging modality for intracranial pathology due to its rapid acquisition time and widespread availability. It is especially valuable for emergency situations, allowing for quick diagnosis and intervention in cases of intracranial hemorrhage, hydrocephalus, or in agitated patients. The use of CT has dramatically increased over the past decade, particularly in emergency settings. Modern CT technology, including volume data acquisition and three-dimensional reconstruction, enhances the assessment of cranial and spinal structures. However, CT has limitations, including exposure to ionizing radiation and reduced sensitivity in the posterior fossa and skull base. The use of nonionic iodinated contrast agents can improve lesion visibility by highlighting areas where the blood-brain barrier is disrupted [39].

8.7.3 Magnetic Resonance Imaging (MRI)

MRI is increasingly utilized for the evaluation of complex CNS disorders due to its superior soft tissue contrast and lack of ionizing radiation. MRI exploits the relaxation properties of hydrogen nuclei in water to generate detailed images. Different pulse sequences highlight various tissue characteristics. In T1-weighted imaging (T1WI), fat appears bright, while water-filled structures such as CSF appear dark. Conversely, in T2-weighted imaging (T2WI), fat appears gray, and water and CSF appear bright. Cortical bone and flowing blood typically produce no signal, known as signal voids. Pathological lesions, which often contain excess free water, appear dark on T1WI and bright on T2WI, making T1WI ideal for anatomical detail and T2WI for pathology detection. The use of paramagnetic contrast agents, such as gadopentetate dimeglumine (Gd-DTPA), enhances the visibility of vascular and intracranial/spinal lesions in post-contrast T1-weighted images [40].

8.7.4 Functional Imaging Techniques

Functional (or physiological) imaging complements structural imaging by highlighting the pathophysiological features of the CNS. These techniques enable the detection of early neuronal injury, evaluate therapeutic efficacy, and guide interventions to reverse or prevent neuronal damage.

- **Perfusion CT Imaging**
  Perfusion CT (PCT) involves dynamic imaging during the rapid administration of iodinated contrast agents, allowing for the assessment of brain perfusion based on changes in contrast agent concentration, measured in Hounsfield units (HU) [41]. Key parameters include:
  1. **Mean transit time (MTT):** The duration between arterial inflow and venous outflow.

2. **Time to bolus peak (TTP):** The interval from contrast injection to peak concentration within the targeted region.
3. **Cerebral blood volume (CBV):** The volume of blood per unit of brain tissue, with normal gray matter ranging from 4 to 6 ml/100 g.
4. **Cerebral blood flow (CBF):** The rate of blood flow per unit of brain tissue per minute, typically 50–60 ml/100 g/min in normal gray matter.

The relationship between CBF and CBV is mathematically expressed as CBF = CBV/MTT. The primary advantage of PCT lies in its broad application and quantitative precision. However, a significant limitation is its inability to image the entire brain in a single scan, generally covering only 2–3 cm of brain tissue per injection. This issue has been somewhat alleviated by the development of 320-slice CT scanners, which enable whole-brain perfusion imaging [42].

- **Diffusion-Weighted MRI (DWI) and Diffusion Tensor Imaging (DTI)**
  Diffusion-weighted MRI (DWI) captures the random movement of water molecules within tissues, known as Brownian motion, to detect microstructural changes. DWI signals are generated based on diffusion properties, with apparent diffusion coefficient (ADC) maps providing quantification of average diffusion rates. Areas of restricted diffusion, such as cytotoxic edema in acute stroke, exhibit increased DWI signal, while regions with enhanced diffusion, like vasogenic edema, show decreased signal.
- DWI is extensively used in diagnosing acute ischemic stroke, where it detects ADC signal reduction and DWI signal increase before conventional MRI reveals abnormalities. It also plays a crucial role in evaluating other CNS conditions, such as abscesses, epidermoid cysts, traumatic brain injury (TBI), and brain development, particularly myelination [43, 44].
  Diffusion tensor imaging (DTI) utilizes the properties of water diffusion to image white matter tracts. While water diffusion in gray matter is isotropic, it is anisotropic in white matter, meaning it occurs preferentially along fiber tracts. Fractional anisotropy (FA) maps, with FA values ranging from 0 (isotropic diffusion) to 1 (maximum anisotropy), and color-coded directional maps enable detailed three-dimensional imaging of fiber tracts [43].
- **Perfusion-Weighted MRI (PWI)**
  Perfusion-weighted MRI (PWI) assesses reversible ischemia and complements DWI, which identifies irreversible infarction. PWI utilizes either exogenous contrast agents or endogenous tracer methods to measure perfusion. Following intravenous gadolinium injection, PWI tracks contrast agent transit through brain capillaries, calculating perfusion parameters such as MTT, TTP, CBF, and CBV [44].
  Arterial spin labeling MRI, which measures brain perfusion without the use of exogenous contrast, employs magnetic pulses to label inflowing water protons. Initially confined to research, this technique is now clinically utilized due to advances in computational speed, particularly benefiting patients with renal insufficiency as it eliminates the need for contrast agents [45].
- **Intraoperative MRI (iMRI)**

Intraoperative MRI (iMRI) aids in precise navigation and tumor resection during neurosurgical procedures. Its implementation has a significant impact on patient management, requiring MRI-compatible equipment to prevent electromagnetic interference and maintain a sterile surgical environment. Research indicates that 65–92% of patients believed to have undergone maximal tumor resection benefit from additional resection guided by iMRI [46]. Three main types of iMRI systems exist: fixed magnet/open patient systems, fixed magnet/movable patient systems, and movable magnet/fixed patient systems. Movable magnet/fixed patient systems are widely adopted, as they allow for the use of non-MRI-compatible equipment while necessitating the patient's movement into the magnet bore for imaging. Fixed magnet/movable patient systems offer similar advantages and can integrate other imaging modalities such as PET and biplane fluoroscopy.

Recent studies suggest that iMRI extends surgical time by approximately 1 h and 47 min. Nonetheless, 42% of patients with presumed complete resection had further resection guided by iMRI [47]. Despite increased costs and surgical time, iMRI reduces early reoperation rates and long-term healthcare expenses.

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