Metabolic Encephalopathy
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This volume is dedicated to Jason, Michael, and James
Preface

The last several years have seen a burgeoning of technical advances in areas of medicine such as imaging and diagnosis, and this trend is sure to continue. These developments have special significance in areas such as internal medicine, neurology, and radiology. The further realization that early diagnosis of disorders which have a biochemical (metabolic) basis has the potential for rapid reversal/improvement, if not outright cure, argues strongly for increased awareness.

One example of reversible metabolic encephalopathy is that seen in thiamine deficiency. Both animal models and humans with “pure” thiamine deficiency develop highly specific neurological symptoms. These symptoms can be reversed completely, or dramatically improved, often within hours, by the administration of thiamine. These results are instrumental in leading to the concept of “metabolic encephalopathy”, a disorder without structural brain changes. From a historical standpoint, there are increasing numbers of such disorders, which are amenable to successful treatment. Sadly, for example, in the case of kernicterus, managed health care has led to an increase in the number of cases due to the early release from hospitals of newborn infants after birth, even before the onset of jaundice.

The area of metabolic encephalopathies is unique in that animal models of disease closely mimic the symptoms seen in human disorders, allowing excellent correlative studies. Seizures are an example of this feature. Many animal models of experimentally induced seizures are available for study in mice and rats, and the neurochemical alterations before and after anticonvulsive therapy can be carefully studied. These more or less direct comparisons permit a more rapid application of results from animal studies to humans.

Given the above, the format for this book is that most chapter contributors have been asked to consider both animal and human studies and to integrate them into statements of mechanisms of biochemical alterations and treatments. The authors have written chapters dealing with the most commonly seen metabolic encephalopathies, and those in which the diagnosis and treatment have advanced and benefited from technological studies. In many cases, it will be seen that there is an underlying alteration in energy metabolism in specific brain regions, which can be documented in animal studies. As the deficit is reversed, the energy metabolites revert toward normal, and the symptoms lessen. Imaging studies in humans support these animal findings, and the rapidity with which this happens argues strongly for
a metabolic lesion, not a structural one. Again, if treated early, structural changes can be minimized, or eliminated from consideration.

These results emphasize another very interesting aspect of metabolic encephalopathies: the diverse anatomical localization of cerebral effects. For example, bilirubin is highly selective in its localization, whereas thiamine deficiency has a completely different localization and is also highly specific. The reasons for this cerebral specificity are largely unclear, but some studies show vastly different metabolism between different brain regions. The cerebellum, for example, is biochemically different from adjacent areas.

In summary, this book on metabolic encephalopathies is meant to combine and correlate animal and human studies. It is hoped that increased awareness of the importance of early diagnosis and treatment of these disorders may result in a lowering of the incidence of structural changes, and morbidity. These disorders hold a special fascination for both basic scientists and clinical investigators because they are accessible, treatable, and there exist good animal models for study. Therefore, this book pulls together basic and clinical neuroscience issues in the treatment of specific metabolic encephalopathies.

This book would not have been possible without the participation and contributions of the many contributors, and I am grateful for their efforts. The editor wishes to acknowledge the expert secretarial and organizational skills of Mrs. Cristina I. Gonzalez and Mrs. Vilmary Friederichs, who have facilitated the production of this book.

We also wish to thank Ms. Ann Avouris of Springer Science and Business Media for her dedicated help in bringing this volume to completion.
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Chapter 1
Functional Anatomy of the Brain

John M. DeSesso

Introduction

The central nervous system comprises the brain and spinal cord which provide sensation, control of movement, emotion, aesthetics, reason and self-awareness. The tissue that makes up the central nervous system is highly differentiated and exceedingly ordered, yet plastic. The central nervous system is well protected throughout by a fluid-filled, tri-layered, connective tissue covering (the meninges) and various osseous claddings. The cranium provides a rigid armor for the brain whereas the vertebral column constitutes the flexible protection of the spinal cord. Because the focus of this volume is the study of various disease states that affect the functions of the brain, it is important to understand the normal relationship of the brain to its surrounding structures including its bony case and its connective tissue coverings, its blood supply, and its internal organization, as well as how the perturbation of the relationships among these structures can impact brain functions. It is the purpose of this chapter to present an overview of this information. More detailed anatomical information is readily available in textbooks of gross anatomy and neuroscience.

Protective Structures

The brain resides within the cranial cavity. The bony roof and sides of the cranial vault make up the calvaria, which is composed of frontal, temporal and parietal bones and a small portion of the occipital bone. The floor of the cranial vault is divided into three depressions or fossae: the anterior fossa extends from the region superior to the orbits and nasal cavity caudally as far as the posterior margin of the lesser wing of the sphenoid; the middle fossa occupies the region between the lesser wing of the sphenoid and the anterior border of the petrous portion of the temporal bone; and the posterior fossa, is underlain by the remainder of the temporal bones and the occipital bone.

Like all bones, those that make up the cranium are invested by a tissue lining, the periosteum. On the interior of the cranial vault, the periosteum is a specialized,
thickened tissue (dura mater) which is the outermost of the meninges that help to protect the brain. Within the cranial vault, the dura mater reflects off the walls of the cranium as horizontal or vertical septa that help to support or restrict the movement of the brain within the cranial vault. Each septum has a free margin. A vertical reflection is a falx; a horizontal reflection is a tentorium. The falces restrict the brain’s lateral movement, as when one turns one’s head too quickly. The falx located between the cerebral hemispheres is the falx cerebri; the smaller one between the cerebellar hemispheres is the falx cerebelli (Fig. 1.1). The tentoria support some regions of the brain and prevent compression of the structures below them. The most important of these is the tentorium cerebelli, which supports the occipital lobe where it overlies the cerebellum. The free margin of the tentorium

Fig. 1.1  (a) Interior of the cranial vault illustrating the major supporting and protective structures, including the cranial fossae. Reflections of dura mater off the calvaria form important structures that help support the weight and restrict the motion of the brain within the cranial vault. (b) Vertical reflections are falces and include the large falx cerebri between the two cerebral hemispheres and the smaller falx cerebelli (not shown) that separates the cerebellar hemispheres. The most significant horizontal reflection is the tentorium cerebelli which supports the occipital lobe of the brain and prevents it from crushing the underlying cerebellum, which resides in the posterior cranial fossa (redrawn after Drake et al., 2005) (See also Color Insert)
cerebelli is a U-shaped opening (the tentorial notch) that allows the brainstem to connect to the rostral regions of the brain, including the thalamus and cerebral hemispheres.

**Organization of the Central Nervous System**

The divisions of the cranial central nervous system include the cerebral hemispheres, the diencephalon (thalamus and hypothalamus), the brainstem (midbrain, pons and medulla oblongata) and the cerebellum (Fig. 1.2). Each cerebral hemisphere occupies one half of the cranial vault and can be subdivided into four lobes (frontal, parietal, temporal, occipital), the insula and the limbic lobe. The first four lobes are named for the cranial bones that overlie them. With respect to the floor of the cranial cavity, the frontal lobes lie in the anterior cranial fossa; the brainstem and cerebellum occupy the posterior cranial fossa; the remaining structures are found either in the middle fossa or within the portion of the cranial vault above the tentorium cerebelli. The insula is covered by the temporal lobe and is not observable unless the temporal lobe is retracted. The limbic system is a continuous interior
Fig. 1.2  Diagrams illustrate the location and relationships of the lobes of the cerebrum and the segments of the brainstem. (a) Lateral view of the gross brain. Note the frontal, parietal, temporal and occipital lobes. The cerebellum is the small region inferior to the caudal region of the cerebrum. (b) Sagittal view that allows one to appreciate the position of the cingulate gyrus (a major constituent of the limbic lobe, which surrounds the corpus callosum and thalamus), as well as the segments of the brainstem: midbrain, pons and medulla. The ventricular system of the brain is also demonstrated. Each portion of the brain has a cerebrospinal fluid-filled cavity at its core, and these cavities are all connected. Cerebrospinal fluid is produced by the choroid plexus within the ventricles and it escapes the ventricular system through foramina in the roof over the fourth ventricle at the pontomedullary junction (See also Color Insert)
structure that surrounds the rostral portions of the brainstem and diencephalon near the midline and is made up of portions of the frontal, parietal and temporal lobes.

The lobes of the cerebrum surround a stalk of nervous tissue that connects the spinal cord with the upper neural centers of the cerebrum. These midline structures include the thalamus and the brainstem. The thalamus protrudes into the middle cranial fossa, above the level of the clinoid processes of the sphenoid bone. It serves as a reciprocal gateway between the cerebral cortex and brainstem that conveys extensive sensorimotor and autonomic information.

Caudal to the thalamus are the midline structures of the brainstem: the midbrain, pons, and medulla oblongata. Dorsal to the pons, but inferior to the tentorium cerebelli, is the cerebellum which is the prominent structure in the inferior cranial fossa. The brainstem as a whole is concerned with somatosensory information from the neck and head as well as the specialized senses of taste, audition and balance. It acts as a conduit for ascending and descending pathways of motor and sensory information between the cortical regions of the brain and the body. In addition, the brainstem is responsible for mediating levels of consciousness and arousal.

The innermost region of the brain consists of a series of connected cerebrospinal fluid-filled cavities, the ventricles (Fig. 1.2). Each cerebral hemisphere contains a lateral ventricle; the midline cavity associated with the thalamus is the third ventricle, which communicates with the lateral ventricles by means of the foramina of Munro. The continuation of the ventricular system caudally through the midbrain is by means of a narrow cerebral aqueduct (of Sylvius), which empties into the fourth ventricle, lying between the ventrally placed pons and medulla oblongata and the dorsal cerebellum. The ventricular system continues into the spinal cord as the central canal. The liquid within the ventricular system is the cerebrospinal fluid, which is made by the highly vascular choroid plexus found within the four ventricles, and which fills the space between the arachnoid and pia mater that surround the central nervous system. The communication to this subarachnoid space occurs through a set of openings located in the roof of the fourth ventricle: the two laterally placed foramina of Luschka and the midline foramen of Magendie. Cerebrospinal fluid flows from its origin at the intraventricular choroid plexus, caudally towards the fourth ventricle where some of it exits the ventricular system to fill the subarachnoid space surrounding the brain and spinal cord. The fluid that invests the brain comes into contact with specialized tissue associated with the venous drainage of the superior aspects of the cerebrum (arachnoid granulations) where, under normal conditions, it enters the venous system, thereby preventing overfilling and distension of the ventricular and subarachnoid systems.

The central nervous system is a tubular structure that is composed of a relatively thick, but highly organized, layer of neuron cell bodies with their attendant cellular processes and numerous supporting glial cells. Populations of neuronal cell bodies are collocated in regions of the central nervous system that look beige (gray matter) when they are observed in the fresh condition. Areas of the central nervous system that contains large amounts of myelinated axons are vanilla-colored or light pink in the fresh condition and are termed “white matter.” In the spinal cord, brain stem and thalamus, white matter is found on the outer surface and gray matter is located deep in the walls of the neural tube. In the cerebrum and cerebellum, gray matter is located
on the surface and the white matter is deep. There are important substructures associated with both the white and gray matters. Bundles of axon fibres that traverse from one region of the central nervous system to another are tracts (also variously called fasciculi, lemnisci, radiations, or commissures — when they interconnect the hemispheres), which are often named for the areas of the central nervous system that they connect. Discrete clusters of neuronal cell bodies are nuclei, most of which have distinct names. For the most part, the neurons in a given nucleus share the same modalities and produce the same neurotransmitter substance.

When viewed in cross-section, the brainstem can be divided into geographically distinct regions, which are identified by means of the relationship of the walls (including both white and gray matter), to the lumen (Fig. 1.3). Thus, the lumen forms the center of the tube and the entire brainstem wall that is dorsal (or superior) to the lumen forms the tectum (from the Latin word for roof). In humans, the tectum remains as a distinct structure only in the midbrain; in the pons and medulla, the large cerebellum arises from the region that would have been the tectum. The territory of the wall that surrounds the rest of the lumen is termed the tegmentum (from the Latin word for covering). The tegmentum does not include all portions of the wall inferior to the lumen, as there are segments of the brainstem (e.g., basilar pons and cerebral peduncles) that have well-developed areas with specific functions and are considered to be distinct from the tegmentum. Throughout the brainstem is a region of gray matter that forms a neuronal mass extending from the rostral spinal cord throughout the brainstem, and into the thalamus and hypothalamus. This ill-defined structure is the reticular formation: a collection of large and intermediate-sized neurons that are loosely arranged into nuclei which form columns that run

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**Fig. 1.3** A cross-section through the midbrain that illustrates the tectum, tegmentum and peduncular regions. Within the wall of the midbrain, note the positions of the periaqueductal gray matter, red nucleus, medial lemniscus, substantia nigra, and territory occupied by the reticular formation. (III nucleus of cranial nerve III, the oculomotor nerve) (See also Color Insert)
parallel to the long axis of the brainstem. The columns are located in the midline (raphe nuclei), just lateral to the midline (the paramedian reticular nuclei), and farther laterally (the lateral reticular nuclei).

The midbrain is of particular importance with regard to auditory and visual reflexes, regulation of arousal, and as a conduit between higher and lower centers of the central nervous system. Consequently, the anatomy of a cross-section of this relatively uncomplicated part of the brainstem will be discussed (Fig. 1.4). The tectum
comprises two pairs of grossly observable elevations (colliculi). The superior colliculi mediate visual reflexes and coordination of head movements and eyes towards a visual stimulus, including those associated with the saccadic movements involved in reading. The inferior colliculi coordinate analogous reflex movements of the head and ears associated with auditory stimuli. The periaqueductal gray matter, which is a descending pathway important in modulating pain, surrounds the lumen of the cerebral aqueduct. The important structures in the tegmentum include the nucleus of the oculomotor nerve (CN III) near the midline; the prominent, orb-shaped red nucleus, which is part of the extrapyramidal motor pathway that controls large muscles of the arm and shoulder; the slit-like substantia nigra which is an essential part of the dopaminergic system (involved in reward and addiction) and whose degeneration underlies Parkinson’s disease; the medial lemniscus, which carries proprioceptive and touch information from the gracile and cuneate nuclei to centers in the thalamus; and the lateral reticular formation which plays a pivotal role in stimulating and maintaining arousal of the upper centers of the central nervous system.

**Vascular Supply**

All arterial blood supply to the brain and brainstem traverses branches of either the internal carotid or vertebral arteries (Fig. 1.5). These arteries, in turn, receive blood from major branches of the arch of the aorta: the internal carotid is a major division of the common carotid artery while the vertebral is derived from the subclavian artery. The blood supply to the brainstem, cerebellum, occipital lobe and the inferior aspect of the temporal lobe is derived from branches of the vertebral system. The frontal, parietal, upper 75% of the temporal lobes and the insular cortex receive their blood supply from the middle and anterior arteries, both of which are branches of the internal carotid system. Although the vertebral and carotid systems supply distinct areas of the brain and brainstem, the two systems are structurally joined by means of a multi-sided system of interconnected vessels (the circle of Willis) located at the base of the brain where they surround the stalk of the pituitary gland, the optic chiasm and optic tracts, and the hypothalamus. The basilar artery (derived from the fused vertebral arteries) terminates as the posterior cerebral arteries. The internal carotid arteries contribute the anterior and middle cerebral arteries and the posterior communicating arteries. The anastomosis is completed by the short anterior communicating artery between the two anterior cerebrials and the paired posterior communicating arteries between the posterior cerebral arteries and the middle cerebral artery. The latter arteries connect the vertebral and carotid blood supplies. Interestingly, the diameters of the arteries vary considerably, especially in the case of the posterior communicating arteries, which frequently may be extremely small on one side or even absent. Consequently, the anastomosis is often only a potential channel and tracer studies in adults have shown that the two blood streams (vertebral and internal carotid) do not mix.
Fig. 1.5 Blood supply to the brain. (a) Vessels that contribute to the arterial circle of Willis at the base of the brain. Note contributions from the vertebral and internal carotid systems. Throughout its length, each vessel that participates in the arterial circle gives off numerous small, unnamed branches that penetrate the brainstem. (b) Distribution of blood supply to the lateral surface of the cerebrum is illustrated. The middle cerebral artery is the prominent vessel, the anterior cerebral artery vascularizes the territory on either side of the falk cerebri and a narrow strip of superior surface of the cerebrum. (c) Sagittal section that depicts the distribution of blood flow to the cerebrum. Note that the anterior and middle cerebral arteries carry blood from the internal carotid arteries, whereas the blood to the posterior cerebral arteries comes from the vertebral/basilar artery system (See also Color Insert)
With regard to tissue blood supply, the organization of the brain and brainstem differs from that of the rest of the body in that there are no anastomoses within the nervous tissue. Each arterial branch is a functional end artery; if it were to be occluded, the territory of the brain that it supplied would become hypoxic and ischemic. Because the blood supply to the brain and brainstem is critical for normal cognitive function, a more complete description of the arterial supply follows.

The vertebral arteries branch from the subclavian arteries in the root of the neck and ascend within the foramina of the transverse processes of six of the cervical vertebrae (C6 – C1). Upon exiting the transverse foramina of C1, the vertebral arteries enter the skull through foramen magnum and approach each other in the midline where they fuse to form the basilar artery at approximately the level of the pontomedullary junction. The basilar artery travels rostrally in a groove on the base of the pons until it terminates as the superior cerebellar and posterior cerebral arteries. The basilar distributes blood via numerous small vessels that enter the pons to supply the pontine nuclei, corticospinal tract, and the pontine portion of the reticular formation. At its termination, the basilar artery gives off the superior cerebellar and posterior cerebral arteries each of which (plus the posterior communicating arteries) gives off numerous small arteries that penetrate the posterior perforated substance to supply the midbrain. Thus, geographically distinct regions of the

Fig. 1.5 (continued)
midbrain receive blood supply from the posterior cerebral, posterior communicating, and superior cerebellar arteries. Each of these arteries gives off numerous small branches throughout their extents; these branches penetrate the nervous tissue to supply the various regions of the brainstem. The approximate areas of vascular distribution are depicted in the diagrammatic representation of a cross-section of the midbrain in Fig. 1.6. The bulk of the lateral midbrain reticular formation is supplied by the superior cerebellar artery; whereas the colliculi, periaqueductal gray matter, and raphe nuclei receive blood from the posterior cerebral artery; and the majority of the cerebral peduncles are vascularized by branches from the posterior communicating arteries.

Functions of Brain Regions

The states of consciousness, cognition and self-awareness are the result of highly complex and integrated functions of the brain. While it may be simplistic to segregate the functions of the brain into discrete activities that are carried out only in specific lobes of the brain, it is clear that regions of the brain that perform similar or related functions are often situated in anatomical proximity to each other.

Fig. 1.6 Cross-section illustrating the distribution of blood to the walls of the midbrain. The tectum is supplied by branches of the superior cerebellar artery. The medial aspects of the peduncular and tegmental regions are vascularized by branches of the basilar artery. The lateral peduncular and tegmental regions are supplied by branches of the posterior communicating artery. Note that these small arteries, which enter the walls of the central nervous system from the periphery, are functional end arteries and do not anastomose with adjacent arteries (See also Color Insert)
Provided that one remains cognizant of the simplification and that the borders of the lobes of the brain were arbitrarily determined by early anatomists, it is possible to observe that motivation and motor functions emanate from the frontal lobe; sensory information is interpreted and integrated in the “association cortex” of the parietal lobe; visual input is decoded and interpreted in the occipital cortex; hearing and declarative memory functions are centered, in large part, within the temporal lobe; and the insular cortex and limbic lobe are central to emotion. Highly complex functions occur at the intersections among these areas. For instance, the precentral gyrus of the frontal lobe (motor cortex) lies parallel to the postcentral gyrus of the parietal lobe (sensory cortex) and the somatotopic organization of these gyri is nearly identical, allowing for the rapid coordination of sensory and voluntary motor functions for given areas of the body. Similarly, functions relating to receptive communication reside in the area where the parietal and temporal lobes abut one another in the dominant hemisphere (Wernicke’s area). Localized damage to specific portions of these areas, regardless of cause, will result in the loss of specific capabilities. As an example, damage to the temporal lobe could result in temporal lobe epilepsy.

The activities that are managed by the various areas of the brainstem are vital for normal functioning of the body and survival, but their control does not reach to the level of consciousness. These brainstem areas include centers in the tegmental pons and medulla that control the performance of cardiovascular, respiratory, and metabolic functions as well as interconnections between the brainstem and the cerebellum and thalami.

The reticular formation is an important structure located deep within the brainstem, which extends rostrally from the upper medulla through the pons and midbrain to the thalamus and forebrain. In its caudal (medullary and pontine) region, the reticular formation contributes to regulation of autonomic functions and to horizontal, conjugate eye movements. The ascending projections of the reticular formation, which traverse the midbrain, contribute to the ascending reticular activating system, which is responsible for controlling the state of arousal of forebrain structures and, thus, one’s level of consciousness. This region is also associated with control of the waking and sleep cycle.

**Physically Induced Alterations in Consciousness**

Given the anatomical and functional complexity of the central nervous system, it is not surprising that a variety of potential problems may afflict individuals with reduced consciousness. These include such possibilities as a generalized reduction in the functions of much of the cerebral cortex due to generalized encephalitis or reduced physiologic functions of the brain due to intoxication or metabolic disease. More geographically restricted pathologies can be caused by vascular disruption or physical compression of portions of the brain. The subject of most of this book will relate to disease states, metabolic disorders and exogenous intoxications (both from
drugs and environmental chemicals). For the purposes of the present discussion, consideration is restricted to the anatomical causes of reduced consciousness.

It is important to note that statements about an individual’s general level of consciousness appear in common usage (e.g., drowsy, lethargic, alert); however, the actual clinical assessment of one’s state of consciousness is a complicated exercise that is beyond the scope of this chapter (see detailed discussions in Weisberg et al., 2004; Plum and Posner, 1972). Nevertheless, it is easy to comprehend the notion that with the progression of a given pathological condition that impacts a region of the brain that is involved with consciousness, one’s ability to respond to environmental stimuli will decrease. Thus, there are grades of impaired consciousness that are associated with various pathological conditions.

With respect to the state of consciousness, the most important configuration is the ascending reticular activating system, the projections of which traverse the midbrain. In general, anatomical causes for reduced levels of consciousness that relate to the central nervous system stem primarily from distortion of the anatomical integrity of important brain structures or, in some cases, compromise of the vascular supply. The former types of lesions can be subdivided into those caused by displacement of structures caused by space filling lesions (e.g., hydrocephaly, tumors, abscesses, hematoma and edema). As any of these lesions increases in size, the intracranial volume available for normal brain tissue is reduced. Eventually, compression of the brainstem results in distortion of the reticular formation with consequent dysfunction that will affect consciousness. Dislodgements of anatomical structures, such as a herniation of the midbrain through the tentorial notch, could also result in the squeezing of the midbrain such that the lateral reticular formation is compromised with consequent impact on arousal. Although dislodgements and displacements result from very different causes, both can ultimately compress internal structures of the brain, triggering symptomatically identical dysfunction.

**Conclusion**

The brain and brainstem are exceptionally complex anatomically, histologically, physiologically, and pharmacologically. Some cognitive functions occur in particular geographic regions with input via axonal projections from other areas of the central nervous system. It is not surprising that myriad perturbations (e.g., vascular, metabolic, inflammatory) can impact their function. Among them is a subset of space-filling lesions that could physically distort the anatomy of the regions that regulate the state of arousal in the cerebrum. This chapter has reviewed the anatomy of the brain and brainstem, with particular attention to the midbrain and the ascending pathways of the reticular formation to call attention to the possibility that impaired consciousness can emanate from pathologies stemming from the distortion of the normal anatomical relationships in the brainstem, and that the outcomes of these pathologies are often identical to those caused by disease states.
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