

DEVELOPMENT  
OF  
NERVOUS  
SYSTEM

- Towards the end of the third week of embryological development in domestic animals, the notochord induces the overlying columnar ectodermal cells of the embryonic disc to become pseudostratified neuroepithelial cells and form a spoon-shaped thickening called the neural plate.
- The cranially expanded region of the neural plate forms the primordium of the brain, while the narrower region, caudal to the brain primordium, gives rise to the neural tube. The raised lateral edges of the neural plate form the neural folds, while the depressed midline region of the plate forms a groove, termed the neural groove.

- Following progressive changes in the columnar neuroepithelium, folding of the neural plate occurs. The cells overlying the notochord become wedged-shaped, with their bases positioned on the basal lamina.
- These changes contribute to the neural plate becoming a V-shaped structure with a midline ventral axis. The neuroepithelial cells in contact with the surface ectodermal cells also become wedge-shaped with their apices positioned on the basal lamina.
- Cellular proliferation at the medial aspects of the neural folds causes these structures to gradually approach each other in the midline, meet and fuse, forming the neural tube which encloses a central neural canal.

- Closure of the neural tube commences at the level of the fourth somite and, from this point, progresses cranially and caudally in a manner similar to the action of a zip fastener. The cranial and caudal ends of the neural tube, which remain patent for a time, are termed the rostral and caudal neuropores respectively. For a short time prior to closure of the neuropores, the neural canal communicates directly with the amniotic cavity.
- As the developing brain and spinal cord have a limited vascular supply at this stage in their development, it has been suggested that these structures receive their supply of nutrients from the amniotic fluid through the neuropores. The rostral neuropore closes midway through the embryonic period with closure of the caudal neuropore occurring shortly afterwards.
- Subsequently, the neural tube loses its connection with the surface ectoderm and occupies a position ventral to the surface ectoderm. The process whereby the neural tube forms by folding, primary neurulation, extends from the rostral neuropore to the caudal neuropore.

- Formation of the neural tube in the sacral and caudal regions of the developing embryo occurs through a process referred to as secondary neurulation. A solid column of mesenchymal cells, derived from the primitive streak in the caudal region of the developing embryo, fuses with the closed caudal end of the neural tube.
- A central canal in this cord of cells, formed by cavitation, becomes continuous with the neural canal formed during primary neurulation. The length of the region of the spinal cord which arises from secondary neurulation is closely related to the number of caudal vertebrae in a given species and, accordingly, is comparatively long in animals with long tails and short in higher primates.

# Dorsal—ventral patterning of the neural tube

- The initial patterning of the central nervous system is regulated by a small number of evolutionary-conserved signalling factor families, expressed as gradients along the cranial—caudal and dorsal—ventral axes.
- The same signalling molecules can induce different effects depending on their concentration, temporal and spatial expression and abundance of relevant receptor families and modulating factors.
- These factors contribute to the development of the gross anatomical structures which comprise the nervous system as well as promoting the differentiation of neural cell subtypes from their pluripotent state.

- When the neural plate has been induced to undergo neurulation by the underlying mesoderm, development of the neural tube commences.
- Two signalling centres, one located in the overlying ectoderm and the other in the notochord, influence the development and formation of the neural tube.
- The neural tube is exposed to gradients of these signalling molecules along the dorsal—ventral axis.

# Neural crest

- During fusion of the neural folds, a population of specialised cells derived from neuroepithelium develops along the lateral margins of the neural folds at the interface between the neural and surface ectoderm.
- These cells are specified by the bone morphogenetic proteins produced at the boundary between the neural plate and surface ectoderm. When induced by these factors, the neuroepithelial cells change their characteristics to those of mesenchyme-like cells and penetrate the basal lamina of the neural plate.
- The microenvironment of the extracellular matrix influences migration of the neural crest cells.
- Neural components derived from neural crest cells include the spinal ganglia, autonomic ganglia and the glial cells of the peripheral nervous system.

# Development of neurons

- Neuroblasts in the dorsal and ventral regions of the mantle layer on either side of the midline proliferate rapidly, resulting in the formation of the left and the right dorsal and ventral thickenings.
- The dorsal thickenings, which form the alar plates, are populated by neuroblasts. Later, these neuroblasts become neurons, referred to as interneurons, which relay sensory impulses. Prominent ventral thickenings which form the basal plates are populated by neuroblasts which give rise to motor neurons.
- Left and right longitudinal grooves form along the inner wall of the central neural canal and each groove is referred to as a sulcus limitans. These grooves demarcate the boundary between the dorsal sensory alar plates and the ventral motor basal plates.
- Due to accelerated cell division, the alar and basal plates expand and the four plates fuse forming the characteristic butterfly-shaped grey area evident in a cross-section of the spinal cord.

# Spinal nerves

- Neuroblasts in the basal plates differentiate, develop cytoplasmic processes and become motor neurons. A number of short processes, known as dendrites, arise at one pole of the neuroblast and, at the opposite pole, a single long process referred to as an axon develops.
- A nerve cell with more than one dendritic process is referred to as a multipolar neuron. From each segment of the spinal cord, axons grow out through the marginal layer of the cord and enter the vertebral canal.
- The ventral roots leave the vertebral canal through the intervertebral foramina on the side from which they derive and innervate effector organs. The sensory components of spinal nerves differentiate from neuroblasts in the spinal ganglia.

# Myelination of peripheral nerve fibres

- Schwann cells, neural crest-derived neurilemmal cells, participate in the myelination of peripheral nerve fibres.
- In this process, neurilemmal cells are described as wrapping themselves around axons, forming a myelin sheath.
- The degree to which the neurilemmal cell becomes wrapped around the neuronal process determines whether a nerve fibre is classified as a myelinated nerve fibre or as a non-myelinated nerve fibre

# Changes in the relative positions of the spinal cord and the developing vertebral column

- Towards the end of the embryonic period the spinal cord is the same length as the vertebral canal, and spinal nerves emerge from the vertebral column through the intervertebral foramina at levels corresponding to their points of origin. During the foetal period, however, the vertebral column grows at a faster rate than the spinal cord.
- Thus, in the late foetal period, the spinal cord is considerably shorter than the vertebral canal and in different species of domestic animals terminates at different levels in the lumbo-sacral region. During this period of development, few if any neurons differentiate in the caudal end of the cord.
- Accordingly, the caudal extremity of the spinal cord tapers and forms a structure which is referred to as the conus medullaris. Caudal to the conus medullaris, the terminal portion of the spinal cord is composed of a cord-like strand of glial and ependymal cells.

# Differentiation of the brain subdivisions

- The cranial expanded region of the neural plate gives rise to three dilations, the primary brain vesicles, namely the prosencephalon (forebrain), the mesencephalon (midbrain) and the rhombencephalon (hindbrain).
- In higher vertebrates, the compact nature of the brain and the relatively small space in which it develops are achieved through the formation of flexures and surface foldings as it is accommodated in the cranium.
- The ventral cranial flexure, which occurs in the midbrain region, is known as the cephalic flexure. The flexure between the hindbrain and the spinal cord is termed the cervical flexure. The prosencephalon gives rise rostrally to the telencephalon and caudally to the diencephalon.
- A narrow central canal persists in the mesencephalon.
- The rhombencephalon forms two dilations, the metencephalon and myelencephalon, both with dilated lumina.

### - Rhombencephalon

- Soon after closure of the neuropores, and as a consequence of the formation of the pontine flexure, the lateral walls of the rhombencephalon splay apart dorsally, stretching the roof plate into a thin rhomboid or diamond-shaped structure, overlying an enlarged central space referred to as the fourth ventricle.

### - Myelencephalon

- The myelencephalon is the most caudal subdivision of the brain. In many respects, the myelencephalon represents a structure which accommodates to the marked morphological differences between the brain and spinal cord, a structure with which it is continuous. It consists of lateral walls each with a dorsal alar and ventral basal plate separated by an intervening sulcus limitans and also a roof and floor. The myelencephalon gives rise to the medulla oblongata.

- Metencephalon

- The metencephalon develops from the cranial region of the rhombencephalon. In a manner similar to the formation of the myelencephalon, the lateral walls of the metencephalon diverge so that the alar plate lies lateral to the basal plate. During its development, the metencephalon differs from the myelencephalon by forming two specialised structures, the dorsally positioned cerebellum and a ventral enlargement, the pons

# Cerebellum

- The dorso-lateral regions of the alar plates of the rhombencephalon, which fold medially, form the rhombic lips.
- The rhombencephalon is a V-shaped structure with the point of the V directed towards the mesencephalon. Thus, the rhombic lips are close together in the region adjacent to the mesencephalon and further apart caudally where they become continuous with the myelencephalon.
- Towards the end of the embryonic period, the rhombic lips proliferate, forming the primordia of the cerebellar hemispheres. As a consequence of continued cellular proliferation, the rhombic lips meet and fuse in the rostral region of the rhombencephalon forming a single structure over the fourth ventricle, the primordium of the cerebellum.

# Mesencephalon

- The mesencephalon undergoes fewer developmental changes than other parts of the developing brain.
- Because of the medial expansion of the alar and basal plates into the roof and floor plates, the neural canal in the mesencephalon is reduced in size, forming the mesencephalic aqueduct.
- The basal plates give rise to two groups of motor nuclei: a medially-positioned general somatic efferent group of cranial nerves III and IV, and a small general visceral efferent group associated with cranial nerve III, located in a more dorsal position.
- The crura cerebri are formed by enlargement of the marginal layer of each basal plate and these structures serve as pathways for nerve tracts descending from the cerebral cortex to lower centres in the pons and spinal cord.

# Differentiation of the prosencephalon or forebrain

- The prosencephalon, the most rostral of the three primitive brain vesicles, gives rise to a caudal diencephalon and a right and left telencephalon.
- From the diencephalon, the optic cups, thalamus, neurohypophysis and epiphysis cerebri are formed.
- The telencephalon gives rise to the cerebral hemispheres and the olfactory bulb.
- The space within the diencephalon is the third ventricle and the paired cavities within the telencephalon are the lateral ventricles.

# Diencephalon

- As basal plates are absent from the forebrain, the diencephalon is formed from the left and right plates and from the roof plate.
- Three swellings, which occur on the medial aspect of the lateral walls of the diencephalon due to cellular proliferation, form a dorsal epithalamic, a middle thalamic and a ventral hypothalamic mass on each side.
- Later, the hypothalamic masses fuse forming a single structure. The thalamus and hypothalamus are demarcated by a hypothalamic sulcus.
- The thalamus undergoes rapid bilateral development and bulges into the cavity of the third ventricle.

# Telencephalon

- The telencephalon, the most rostral derivative of the prosencephalon, consists of a central portion, the lamina terminalis, and two lateral diverticula, the walls of which form the future cerebral hemispheres.
- The cavities of these two diverticula, the lateral ventricles, communicate with the lumen of the diencephalon, the third ventricle, through the inter-ventricular foramina. Initially, the openings between the lateral ventricles and third ventricle are wide.
- Later, with the expansion and growth of the cerebral hemispheres, the lumen of each inter-ventricular foramen decreases in size.
- The developing telencephalic vesicles extend initially in a rostral direction.

# Ventricular system of the brain and cerebrospinal fluid circulation

- The cavities of the brain vesicles and the lumen of the neural tube persist and subsequently give rise to the ventricular system of the brain and the central canal of the spinal cord respectively.
- The ventricles and the central canal, lined by ependymal cells, contain cerebrospinal fluid. The lateral expanded cavities of the telencephalic outgrowths are termed the left and right lateral ventricles.
- The central cavity of the telencephalon and the cavity of the diencephalon form the third ventricle which surrounds the interthalamic adhesion of the diencephalon.
- The central lumen of the mesencephalon remains narrow and forms the mesencephalic aqueduct, while the expanded cavity of the hindbrain forms the fourth ventricle.

# Blood–brain barrier

- The immediate environment of brain cells is further protected by the blood–brain barrier which assists in regulating the composition of the extra-cellular fluid.
- The capillaries of the brain, unlike capillaries in other organs of the body, act as a selective barrier which excludes macromolecules. These capillaries permit passage of most plasma constituents except proteins.
- This selective exclusion of macromolecules is attributed to the arrangement of endothelial cells of capillaries which have tight junctions.
- The perivascular feet of astrocytes, which are attached to the basal lamina of capillaries of the nervous system, may also contribute to the formation of a selective barrier.

# Brain stem and spinal cord

- When developmental features of the brain stem are examined more closely, it becomes evident that the primitive brain stem consists of a dorsal sensory alar plate and a ventral motor basal plate on each side, demarcated by a sulcus limitans.
- In common with the spinal cord, the cranial alar and basal plates give rise to general somatic afferent, general visceral afferent, general visceral efferent and general somatic efferent columns of neural tissue which contribute to the grey matter of the brain stem.
- Similarities in the basic structure of the brain stem and spinal cord during early development become altered by developmental changes which modify the architecture of the brain stem.
- These changes include the lateral folding of the walls of the hindbrain so that the alar plates are positioned lateral to the basal plates with enlargement of the central neural canal.

# Cranial nerves

- Twelve pairs of cranial nerves develop in mammals. By convention, Roman numerals are used to designate the cranial nerves according to their sites of origin in the brain, with cranial nerve I the most rostral and cranial nerve XII the most caudal.
- Cranial nerves are also named in accordance with the regions or structures which they innervate or serve. Thus, cranial nerve I is also known as the olfactory nerve.
- Although they have some features in common, spinal nerves and cranial nerves also exhibit some fundamental differences. Because spinal nerves have sensory and motor components, they are referred to as mixed nerves.
- In contrast, the cranial nerves can be classified according to their functions and their embryological origins into three categories, namely nerves with special sensory functions, nerves which have exclusively motor functions and those which innervate pharyngeal arch derivatives, which are mixed.

# Special sensory nerves

- Three cranial nerves, namely olfactory (cranial nerve I), optic (cranial nerve II) and vestibulocochlear (cranial nerve VIII), are included in this category.
- The olfactory and optic nerves are often regarded as extensions of brain tracts rather than true cranial nerves.

# Cranial nerves with exclusively motor functions

- The oculomotor, trochlear and abducent nerves, cranial nerves III, IV and VI respectively, innervate the extrinsic muscles of the eyeball.
- The hypoglossal nerve, cranial nerve XII, innervates the lingual muscles and the tongue. Unlike cranial nerves IV, VI and XII, which are exclusively somatic, cranial nerve III also carries general visceral efferent fibres which innervate the ciliary muscles.
- Although these four cranial nerves are usually classified as having exclusively motor function, they may, in addition, contain fibres associated with proprioception which relay sensory information from muscles and joints.
- Unlike the cell bodies of other sensory systems which are located in spinal ganglia, the cell bodies of these afferent proprioceptive fibres are located within their respective nerve trunks.

- Cranial nerves with both sensory and motor function

- Four cranial nerves, the trigeminal (cranial nerve V), facial (cranial nerve VII), glossopharyngeal (cranial nerve IX) and vagus (cranial nerve X) innervate pharyngeal arch derivatives. As these nerves carry both sensory and motor fibres they are classified as mixed nerves.

- Peripheral nervous system

- The peripheral nervous system comprises the components of the nervous system which are located outside the brain and spinal cord. This system consists of cranial and spinal nerves, associated sensory and autonomic ganglia and their non-neuronal supportive cells. The afferent fibres arise from spinal ganglia, while the efferent fibres arise from multipolar neurons in the basal plates of the developing spinal cord or brain stem. The spinal, cranial and autonomic ganglia and their associated glial cells arise from the neural crest. Some neurons of the cranial ganglia develop from placodes.

# Autonomic nervous system

- The autonomic nervous system is that subdivision of the nervous system which regulates many of the involuntary activities of the body.
- It has afferent, central and efferent components, with overall regulation by the hypothalamus.
- This system has a central regulatory role in the functioning of smooth muscle, cardiac muscle, exocrine glands and some endocrine glands.
- The autonomic nervous system can be further subdivided into a sympathetic system and a parasympathetic system on the basis of anatomical and physiological features

# Sympathetic nervous system

- Towards the end of the embryonic period, neural crest cells on either side of the spinal cord migrate to positions lateral to the developing vertebrae where they form aggregations.
- From these aggregations, segmentally arranged paravertebral ganglia of the sympathetic nervous system develop.
- Initially, these paravertebral ganglia are distributed along the length of the vertebral column from the cervical to the sacral region, alongside the body of each vertebra.
- The eight paravertebral ganglia in the cervical region form three aggregations

# Parasympathetic nervous system

- Pre-ganglionic neurons of the parasympathetic system are located both in the brain stem, where they form distinct nuclei, and also in the lateral columns of the sacral region of the spinal cord.
- The pre-ganglionic parasympathetic axons which emerge from the brain stem as components of the oculomotor, facial, glossopharyngeal and vagus nerves, innervate tissues and structures of the head.
- In addition to innervating cranial structures, the vagus nerve innervates viscera in the thoracic and abdominal cavities.
- The pelvic nerve is formed from the pre-ganglionic axons of the sacral nerves.
- The ganglia of the parasympathetic system, which develop from neural crest cells, are referred to as terminal or intramural ganglia.

# Enteric nervous system

- A system of neurons, nerve fibres and supporting cells, distributed in the submucosal connective tissue and between the layers of the muscularis externa, innervates enteric tissue and some associated structures.
- The enteric nervous system is composed of reflex pathways which influence gastrointestinal motility and secretion, movement of water and electrolytes across intestinal epithelium and the regulation of intestinal blood flow.
- Neurons of the enteric nervous system derive from neural crest cells originating in the hindbrain region, referred to as vagal neural crest cells, with possible contributions from sacral neural crest cells

# Meninges

- Along its entire length, the developing neural tube is surrounded by loose mesenchymal tissue. Subsequently, this mesenchymal tissue condenses, forming the protective coverings of the central nervous system, the meninges.
- These coverings develop into an outer ectomeninx, considered to be a derivative of the axial mesoderm, and an inner layer, the endomeninx, derived from neural crest cells.
- The ectomeninx forms the dura mater, a tough, white, fibrous, tubular connective tissue sheath composed of collagen and elastic fibres.
- Along the length of the spinal cord, extensive attachments do not develop between the dura mater and the surrounding developing vertebrae so that, in its final form, the dura mater has osseous attachments only at its cranial and caudal ends.

