

4. Development of nervous system. Neural plate. Brain vesicles. Sensory organs.

Development of the central nervous system

- neurulation = ectoderm in front of the primitive node thickens to form the **neural plate** (week 3, day 17-18)
- neural plate bends to form a **neural groove** in the middle
- the borders are bulging as the neural **folds**
- the neural groove invaginates and closes to form the **neural tube;** the closure of the neural tube starts in the cervical region and proceeds towards the cranial (anterior) neuropore and the caudal (posterior) neuropore; the neuropores are last segments to be closed (the cranial neuropore on day 25, 18-20 somitic embryo; the caudal neuropore on day 27)

Segmentation of the neural tube

- a series of thickenings and constrictions = neuromeres → regional segmentation
- the caudal segment develops into the spinal cord
- the cranial segments for the brain vesicles
  - **prosencephalon** (forebrain), which will futher differentiate into
    - **telencephalon**
    - **diencephalon**
  - **mesencephalon** (midbrain)
  - **rhombencephalon** (hindbrain), which will further be divided into
    - **metencephalon**, which forms the
      - pons Varoli
      - cerebellum
    - **myelencephalon,** which becomes the medulla oblongata
- there are flexures: cephalic flexure in the mesencephalic region; pontine flexure between the metencephalon and myelencephalon; cervical flexure between the metencephalon and the spinal cord

Histogenesis of the neural tube

- histogenesis starts with the pseudostratified columnar epithelium of the primitive neural tube → neuroblasts and gliablasts
- **neuroblasts** = precursors of neurons
  - temporarily apolar neurons, forming primitive dendrites and axon → bipolar and multipolar neurons
  - the bodies neuroblasts form the grey matter
  - the nerve processess of the neuroblasts form the white matter
- **gliablasts** (spongioblasts) = precurors of glia cells
  - in the mantle layer they differentiate into plasmatic and fibrillar astrocytes
  - oligodendrocytes form myelin sheaths surrounding the axons and dendrites of the neurons
  - periventricular neuroepithelium → ependymal cells lining the CNS cavities
  - *(microglia cells do not originate from the neuroepithelium, but they migrate into the CNS from the mesenchyme)*
- proliferation of neuroblasts → thickening of the neural tube:

- **ventral basal plate** = motoric region of the spinal cord; contains ventral motor horns with efferent motor neurons
  - medial somatomotoric nuclei of the cranial nerves XII, VI, IV, III
  - lateral somatomotoric nuclei of the cranial nerves IX, X, XI, VII, V
  - visceromotoric nuclei: preganglionic parasympathetic neurons of the cranial nerve IX, X, VII, III
- **dorsal alar plate** = sensory area; dorsal horn with afferent sensory neurons entering the spinal cord from the dorsal root of the spinal nerves
  - lateral sensory nucleus: n. VIII,
  - somatosensory nucleus: n. V.
  - viscerosensory nuclei: n. V, n. VII, n. IX, n. X
- sulcus limitans separates the basal plate from the alar plate
- the right ant the left alar plates are connected by the dorsal roof plate
- the right ant the left basal plates are connected by the ventral floor plate
- the lateral horns develop in the region Th1-Th12 and L1-L3 (thoraco-lumbal sympathetic nervous system)

Positional changes of the spinal cord

- in the 3rd month the spinal cord extends the entire length of the body
- the vertebral column and the dural sac lengthen more rapidly than the neural tube → disproportionate growth → spinal nerves run obliquely
- the dura remains attached to the vertebral column → the dural sac
- the spinal cord in newborns extends to the body of the L3 vertebra
- extension of the pia mater = filum terminale internum
- in the adult, the spinal cords extends to the L1/L2 level (in male) or to the L2 level (female), whereas the dural sac continues to the S2 level→ lumbar puncture of the subarachnoideal space is to be done between L3/L4 (or L4/L5)

Brain

- **telencephalon**
  - lamina terminalis in the middle, hemispheres are lateral
  - lateral ventricles develop within the cerebral hemispheres; they communicate via the interventricular foramen of Monro with the 3rd ventricle
  - basal regions of hemispheres are bulging into the lateral ventricles as the basal ganglia
  - ependyme and the vascularised mesenchyme forms the choroid plexus of the lateral ventricles
  - hippocampus is also bulging into the lateral ventricles
  - hemispheres are growing over the diencephalon, mesencephalon and the cerebellum
  - pallium = cell layer on the surface of hemispheres
    - paleopallium in the region lateral to the corpus striatum → paleocortex with 3 layers
    - archipallium in the medial part → archicortex with 3 cell layers
    - neopallium covering most of the hemispheres → 6 layers of the cerebral neocortex
  - migration waves of neuroblasts proceed towards the brain surface → cortical cytoarchitectonics emerges

  - commissurae cerebri connecting the hemispheres (anterior, hippocampal/fornix commissure, corpus callosum); posterior and habenular commissure
- **diencephalon**
  - its cavity → 3rd ventricle; the roof forms the tela choroidea ventriculi III.
  - epithalamus with the epiphysis (melatonin, circadian rhythms)
  - thalamus and its nuclei connecting pathways to the brain cortex
  - growth of the thalamus → bulging into the 3rd ventricle → adhesio interthalamica in the midline
  - hypothalamic nuclei involved in homeostatic regulations
  - infundibulum → neurohypophysis (joining the Rathke's stomodeal pouch → hypophysis)
  - diencephalon → connected with the optic vesicles via the nerve II
- **mesencephalon**
  - its cavity → aquaeductus mesencephali (Sylvii)
  - basal plate with motor nuclei
  - there are the crura cerebri below the basal plate, they contain axons connecting the brain cortex with the spinal cord
  - anterior (superior) colliculus (reflex centres for visual reflexes); posterior (inferior) colliculus (synaptic relay for auditory reflexes)
  - nucleus ruber and the substantia nigra
- **pons**
  - contains pathways connecting the brain cortex, cerebellum, and spinal cord
  - the basal plate has three rows of nuclei of cranial nerves and nuclei of the reticular formation
  - the alar plate contains sensory nuclei and also the pontine nuclei (connecting fibres between the brain cortex and the cerebellum)
- **cerebellum**
  - vermis in the midline; lateral hemispheres cleaved with parallel grooves
  - migration of neuroblasts → three layers of the cerebellar cortex; other cells differentiate into the neurons of the cerebellar nuclei
- **medulla oblongata**
  - unlike the spinal cords, the alar plates are laterally widely open
  - the basal plate has three groups of motor nuclei
  - alar plate has three groups of sensory nuclei
  - the central canal in the middle connects the brain cavities with the central canal of the spinal cord

Neural tube defects

- a broad range of defects affecting the spinal cord, meninges, vertebrae, vertebral muscles or the skin; some of them may be prevented by folic acid
- spina bifida = a neural tube defect affecting the spinal region
  - spina bifida occulta: a defect of fusion of vertebral arches; does not involve spinal cord defects; usually causes no symptoms; mostly in the lumbosacral region
  - spina bifida cystica: a severe defect with neural tissue and/or meninges protruding through a defect in the vertebral arches and skin
    - meningocele = herniation of the meninges

    - meingomyelocele = herniation of the meninges and nervous tissue (which is damaged)
    - abnormal fixation of the spinal cord within the vertebral canal → displacement of cerebellum into the foramen magnum (Arnold-Chiari syndrome) → the cerebrospinal fluid flow is blocked → hydrocephalus
    - myeloschisis and rhachischisis = the neural tube fails to close
- holoprosencephaly: the telencephalon and the face fails to divide
- exencephaly, anencephaly – the cranial neuropore fails to close → the skull vault is missing → the brain is not covered and protected
- hydrocephalus with abnormal accumulation of cerebrospinal fluid; mostly caused by an obstruction of the aquaeduct of Sylvius) → skull bones are expanding

Myelination

- in the CNS: processes of oligodendrocytes; starts in month 4, continues after birth up to 2 years (and extends even later into the childhood)
- in the PNS: Schwann glia cells, since month 4

Cranial nerves

- their nuclei appear already in the week 4
- n. I originates from the telencephalon; n. II from the diencephalon; n. III in the mesencephalon; the remaining cranial nerves develop within the brain stem
- somatomotoric nuclei of nerves IV, V, VI, VII, IX, X, XI, XII
- visceromotoric nuclei of nerves VII, IX, X
- sensory ganglia of cranial nerves originating from ectodermal neural placodes and from the neural crest: nerves I, VIII, V, VII, IX, X
- parasympathetic ganglia of nerves III, VII, IX, X

Neural crest

- originates along the neural folds (except of the prosencephalic region)
- its cells disseminate and migrate into the periphery since the week 4 to contribute to a number of structures, i.e.:
    - in the head and neck region
        - cranial nerve sensory ganglia and ganglia of nerve V, VII, IX, X
        - ectomesenchyme of the branchial arches
        - odontoblasts
    - the aortico-pulmonary septum
    - in the thoracolumbar region:
        - the dorsal root spinal ganglia
        - postganglionic autonomic neurons of the enteric nerve system
        - the medulla of the suprarenal glands
        - melanocytes
    - Schwann cells

The ear

- internal ear
    - thickened ectodermal in the rhombencephalic region = otic placode
    - the otic placode invaginates and forms a hollow otocyst (otic, auditory vesicles)

  - the otocyst differentiates into a membranaceous labyrinth lined with an epithelium
    - ventral saccule
    - cochlear duct grows from the saccule and contains the organ of Corti
    - dorsal utricle branching into semicircular canals and the endolymphatic duct
- middle ear
  - the tympanic cavity originates mainly from the entoderm of the 1st pharyngeal pouch and therefore communicates with the nasopharynx via the Eustachian tube
  - auditory ossicles: malleus and incus originate from the 1st mandibular pharyngeal cartilage; the stapes originates from the 2nd pharyngeal cartilage
- external ear:
  - the auricle develops from six mesenchymal proliferations (auricular hillocks) surrounding the 1st pharyngeal cleft
  - the external auditory meatus develops from the first pharyngeal cleft
  - the eardrum has an ectodermal lining, connective tissue layer, and an entodermal epithelium

Eye

- optic vesicles and the lens
  - the wall of the diencephalon forms lateral outpocketings in the week → optic vesicles
  - the vesicles grow laterally and invaginate into optic cups that induce thickening of the surface ectoderm = the lens placode
  - the lens placode invaginates and forms a lens vesicle (week 5) which migrates deeper into the optic vesicle
  - the posterior epithelial cells of the lens grow towards the anterior epithelium, thus filling the cavity of the lens vesicle and forming a solid lens
  - the rest of the surface ectodermal optic placode differentiates into the cornea
- retina
  - the outer layer of the optic cup becomes the pigment layer of the retina
  - the inner layer of the optic cup becomes the neural layer of the retina and differentiates into three layers of neurons (photoreceptors=rods+cones, bipolar neurons, ganglion cells) and layers of neuroglia
- the iris, the ciliary body and the choroid represent the vascular layer of the eyeball and they differentiate from the vascularised mesenchyme
- the fibrous layer of the eyeball differentiates from the mesenchyme: the sclera (dense irregular collagenous connective tissue), the cornea (avascular stroma covered with the outer ectodermal epithelium and with the inner endothelium lining the anterior chamber)
- the hyaloid artery (from the ophthalmic artery, which branches from the internal carotid art.)
  - supplies the retina and the lens; runs through the vitreous body
  - the retinal part persists → the central artery of the retina
  - the lenticular plexus disappears, leaving a hyaloid canal within the vitreous body
- the optic nerve
  - represents the optic stalk connecting the optic cup with the diencephalon
  - the optic stalk has a ventral groove surrounding the hyaloid artery (and vein)

- choroid fissure = a temporary groove on the ventral surface of the optic stalk; this has to close in the week 7 and the hyaloid artery (later the central artery of the retina) becomes entrapped within the optic nerve

– eye abnormalities
  - coloboma iridis = the choroid fissure fails to close; it may affect the iris, the ciliary body, the retina, or even the optic nerve
  - persistence of the iridopupillary membrane
  - inborn cataracta of the lens
  - persistence of the hyaloid artery
  - microphalmia (frequently caused by intrauterine infections)
  - anophtalmia
  - aphakia = absence of the lens
  - cyclopia, synophtalmia = due to a loss of midline issue, the optic cups and the eyes merge in the midline; it is associated with holoprosencephaly (merged hemishperes of the telencephalon)