Development of the Nervous System

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Overview

• How does CNS development begin in embryo

• What changes in shape and what processes allow the CNS to achieve its final form

• How are axons guided on their long journey to destinations

• What changes occur postnatally

• Where can errors occur

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http://neuroscience.uth.tmc.edu/s2/chapter01.html
Objectives

1. Describe the formation and fate of the neural tube and neural crest.

2. Name and describe the formation of the primary and secondary embryological compartments of the CNS. Describe what they represent in the adult CNS.

3. Understand the role of growth factors and other molecular signals during development.


5. Understand postnatal mechanisms that result in maturation of the CNS (myelination, synaptogenesis, dendritic pruning, critical period).
CNS Development
In the Beginning……..

- **Ectoderm** thickens
- Invagination forms
  - neural groove
  - neural folds
- Groove deepens
- Folds close
- Neural tube separates

Day 15

Neural Folds become neural crest forming PNS ganglia, schwann cells

Day 28

Neural Tube becomes CNS
Early Developmental Defects

• Failure of the neural tube to close or separate from surface ectoderm:
  • caudally—spina bifida
  • rostrally—anencephaly
In the Beginning... The Movie
Weeks 4 - 6

• Neural tube expands and bends to form 3 chambers:
  • Prosencephalon
  • Mesencephalon
  • Rhombencephalon

• 3 chambers transform into 5 secondary chambers:
  • Telencephalon
  • Diencephalon
  • Mesencephalon
  • Metencephalon
  • Myelencephalon
Fate of Developmental Compartments

- **Prosencephalon**
  - Telencephalon
  - Cerebral Hemispheres and Lateral Ventricle
  - Diencephalon
  - Dorsal Thalamus + Epi, Hypo, Sub, Thalamus, Posterior Pituitary, 3rd Ventricle, *Visual System*

- **Mesencephalon**
  - Mesencephalon
  - Midbrain and Cerebral Aqueduct

- **Rhombencephalon**
  - Metencephalon
  - Pons, Cerebellum, rostral half of 4th Ventricle
  - Myelencephalon
  - Medulla, caudal half of 4th Ventricle
Development After Week 3

Starting with a simple tube, a complex structure (brain) forms rostrally, but simple structure (spinal cord) caudally.

After neural tube forms, growth occurs by:

- proliferation
- migration
- bending (shapes brainstem and repositions ventricular system.)
Developmental Transformation

250,000 neurons/minute born!
Threats to Prenatal Development

- **Teratogens** can impair early prenatal development
  - Timing and amount influence the magnitude of defect.
  - alcohol
  - accutane/retinoic acid) affect CNS development
  - thalidomide/sedative
  - antiseizure meds

- Thyroid function – maternal thyroid hormone influences neuronal migration, synaptogenesis, and myelination.
Internal Development - Spinal Cord and Brainstem

Proliferation, migration

Sensory neurons

Motor neurons
Nerve Cells – Divide and Conquer

• Not only increasing in number, but also extending axons/dendrites to invade areas.

• How is the pattern of nerve pathways in the CNS and PNS achieved?
Axon/Dendrite Growth

- Nerve cells extend axons/dendrites by *growing at their tips*

- The *length and branching* of axons and dendrites make them different from all other cells.

- Axon/dendrite extension is *guided* by molecular signals that convey *adhesion, attraction, repulsion*
Axon Guidance Signals

1. Growth Factors
   • survival, axon guidance

2. Extracellular Matrix Molecules
   • provide adhesive substrate - growth

3. Cell Adhesion Molecules
   • cell-cell adhesion

4. Secreted and cell surface molecules
   • growth/guidance signals
Axon Guidance Signals

4. Secreted and cell surface molecules

Guidance molecules released by cells near the midline of the spinal cord attract axons toward the opposite side, producing a normally crossed pathway. Mutations cause deficits in limb movements due to mis-guided axons.
Growth Factors

• An important developmental process: matching the number of nerve cells in a population with the size of its target.
  • Typically, a 2-3x surplus of nerve cells is produced
  • Survival is determined by competition for synaptic contact
  • Only those neurons that form a synaptic contact receive a limited supply of growth factor from target.
• Neurons become dependent on factors over lifetime
• Secreted by neurons, target organs, glia, fibroblasts, macrophages, muscle, ……

Target organ
Growth Factors

- Examples: NGF, BDNF, NT-3, CNTF, GDNF……..
- Each neuronal population requires specific type factor
- Survival dependence more apparent for PNS.

**Important Questions:**

- Are neurodegenerative diseases caused by loss of growth factors in adults?
- Therapeutic use of growth factors to rescue dying neurons? (Little positive evidence so far!)

Alzheimers  Loss of hearing/vision

MS  Lou Gherigs  Parkinsons
This demonstrates a fundamental aspect of NS:

Rather than genetic programming, the NS depends on interactions with its surrounding environment for its form and function. It reduces the amount of information that must be programmed into nerve cells for their development.
Organization of Hemispheres

- Cell Bodies (gray matter) – in a thin layer of outer cortex
- Axons (white matter) – in fiber layer under cortex
- Some cell bodies (gray matter) – buried deep in the fiber layer

How do the nerve cell bodies get positioned on the surface?
Organization of Cortex

Most cortex has 6 layers.

Cell body stain, myelin unstained.

2. How do the cortical layers form?
Organization of Cortex

Organization of cortical layers is critical to how the cortex receives, processes, and transmits information.

Inability to form normal layers leads to deficits - seizures, mental retardation.
Cortical Development

- Transforming the embryonic telencephalon into adult cortex requires proliferation and migration

1. Increases brain mass
2. Cell bodies migrate from ventricular to outer surface to form cortex
3. Cortical layers form
Cortical Development

- Differentiating neurons migrate to surface to form:
  - cortex with 6 layers (grey matter)
  - deeper, thick region of fibers (white matter)

SubVentricular Zone - remains important area for stem cells in adults.
Cortical Development

Proliferation and migration are important in producing cortical layers and in sculpting the pattern of sulci, gyri and fissures.
Cortical Development

Defects in proliferation/migration cause disorders:

• *Microcephaly* - small brain size
• *Polymicrogyria* - small gyri
• *Lissencephaly* - smooth; abnormal layers
• *Heterotopia* - misplaced gray matter

These often result in epilepsy, mental retardation, or death.
Postnatal Development

• How does the brain change after birth?

• By year 2 – *triples in weight; 3/4 adult size*

  What’s happening?

No new neurons born, but how to explain the cognitive and behavioral changes occurring from birth to 2 years old!!
Postnatal Development

• Brain growth and new functions due to 3 processes:
  1. **Myelination** – signal conduction
  2. **Dendritic Growth/Pruning** – inputs
  3. **Synapse Formation/Elimination** – communication

• *These processes are all influenced by electrical activity, ie environmental stimulation/experience.*

Each neuron receives **1000 - 10,000 synapses** creating **100 trillion connections**

1. Not enough info in DNA
2. Function based on experience
Postnatal Development

The shaping of neural circuits fundamental to normal brain function requires a rich interaction between an infant and its environment.
Postnatal Development

• Postnatal brain function is largely shaped during **critical periods** – times when neural circuits are especially capable of dendritic and synaptic reorganization that establishes their capacity to process information.

• Appropriate **stimulation** (sensory, motor, other?) at specific developmental stages determines later functional capabilities.  

• **Stress hormones** can impair brain maturation with long term consequences in behavioral, emotional, cognitive deficits.

**Catarract in newborn** vision, hearing, language…
All of this results from the requirement for experience in shaping the postnatal development of brain circuits.

These processes persist throughout life – experience shapes brain function.