Medical Neuroscience | Tutorial Notes

Early Brain Development

MAP TO NEUROSCIENCE CORE CONCEPTS[1]

NCC2. Neurons communicate using both electrical and chemical signals.

NCC3. Genetically determined circuits are the foundation of the nervous system.

NCC4. Life experiences change the nervous system.

LEARNING OBJECTIVES

After study of the assigned learning materials, the student will:

1. Characterize the events that occur during gastrulation and neurulation.
2. State the significance of induction for the initial development of the CNS.
3. Discuss the factors the guide migrating neuroblasts to their final destinations in the developing gray matter structures of the CNS
4. Characterize the cellular mechanisms that influence the differentiation of neurons and glia in the CNS.
5. Describe the role of apoptosis in CNS development.

TUTORIAL OUTLINE

I. Introduction

- A. mechanisms of neural development
  1. **genetic specification:** lineage-derived signals expressed via gene transcription
  2. **self-organization:** cell-cell interactions mediated via molecular and activity based mechanisms
  3. **sensorimotor experience:** environmental interactions expressed later in neural development (once sensory and motor systems become functional) and throughout life
- B. each of these basic mechanisms is subject to modification due to the consequences of genetic mutation, disease, exposure to environmental and dietary toxins, or normal and abnormal use (sensorimotor experience)

[1] Visit **BrainFacts.org** for *Neuroscience Core Concepts* (©2012 Society for Neuroscience) that offer fundamental principles about the brain and nervous system, the most complex living structure known in the universe.

1. most major congenital malformations of the CNS occur as a result of dysfunction in the expression of genetic specification or the cell-cell interactions that give rise to ordered patterns of structure and connectivity in neural circuits
2. in later stages of brain development, sensorimotor experience should be considered an important factor in neurological function/dysfunction

II. Initial Formation of the CNS

A. **Gastrulation**

1. invagination of the developing blastula that produces three germ layers:
   a. ectoderm (outer layer): *gives rise to the entire nervous system!*
   b. mesoderm (middle layer): forms muscle, skeleton, connective tissue, cardiovascular and urogenital systems
   c. endoderm (inner layer): forms gut and associated viscera
2. forms the **notochord** along the dorsal midline of the embryo from mesoderm; this transient structure defines the midline, the plane of bilateral symmetry, and the principle axes of the embryo (anterior-posterior; dorsal-ventral; medial-lateral)

B. **Neurulation** (3-4 weeks of gestation)

1. formation of the neural plate and its subsequent folding upon itself to form the neural tube (**Figure 22.1**[2])
   a. the notochord gives rise to chemical signals that "induce" the differentiation of neural precursor cells in the overlying ectoderm

> ***Induction*:** The ability of a cell or tissue to influence the fate of nearby cells during development by the synthesis and secretion of chemical signals (peptide hormones) that modulate gene expression. *The specificity and precise timing of inductive signaling is crucial for normal development.*

   b. this special part of the ectoderm becomes a distinct columnar epithelium called the **neural plate**
2. the lateral margins of the neural plate fold inward and then seal off to form the **neural tube**
   a. the neural tube differentiates into the entire CNS
      i. all cellular components of the CNS are derived from the epithelium of the neural tube
      ii. the lumen of the neural tube becomes the ventricular spaces of the mature brain and spinal cord

[2] Figure references to Purves et al., *Neuroscience, 5th Ed.*, Sinauer Assoc., Inc., 2012. [click here]

b. the notochord continues to provide an inductive influence as the ventral portion of neural tube differentiates into the **floor plate** (see Figure 22.2)

i. in turn, inductive signals arise from the floor plate and influence the differentiation of neural precursor cells in the ventral parts of the neural tube

ii. some cells in these regions eventually become the motor neurons and interneurons of the brainstem and spinal cord

c. at the other side of the neural tube, dorsal neural precursor cells are induced to form the **roof plate**, which in turn induces the formation of sensory system neurons of the brainstem and spinal cord

d. a third special region of the neural tube, also along the dorsal midline, differentiates into the **neural crest** (see Figure 22.2)

i. neural crest cells migrate away from the neural tube

ii. along the way, they are influenced by a broad spectrum of chemical signals that determine their migratory fate and ultimate identify

iii. neural crest progeny give rise to all the neurons and glia of the peripheral nervous system, the neurosecretory cells of the adrenal medulla, the neurons that constitute the enteric nervous system, and other non-neural cells (see Figure 22.11)

e. several congenital malformations of the CNS result from a failure of the neural tube to complete seal (e.g., spina bifida, anencephaly)

III. Formation of Major Subdivisions of the CNS (3-4 months of gestation)

A. morphological alterations of the neural tube (see Figure 22.3)

1. rapid and disproportionate cellular proliferation together with movements that bend, fold and constrict different parts of the neural tube give rise to the major subdivisions of the embryonic brain

2. after the initial formation of the major subdivisions of the embryonic CNS, additional partitioning of the **prosencephalon** establishes the early **telencephalon**, **diencephalon** and the optic cups, which give rise to the retina

3. similarly, the **rhombencephalon** partitions into the **metencephalon** (cerebellum and pons) and the **myelencephalon** (medulla oblongata)

review the relation between structures in the adult brain and their embryological origins; see Table A24

4. these regional changes that shape the developing neural tube are influenced by the spatial and temporal expression patterns of **homeotic genes**

a. in fruit flies, homeotic genes encode DNA-binding proteins that guide the differentiation of the embryo into distinct segments, defining the anterior-posterior axis of the body plan (see Figure 22.4)

b. similar genes, called **Hox genes**, have been found in mammals, including humans

c. like homeotic genes, Hox genes encode DNA-binding proteins that modulate the expression patterns of other genes; these proteins are important mediators of neural induction

i. in humans, we have four clusters of Hox genes, with each on a different chromosome

ii. their expression contributes to the cellular and molecular processes that eventually produce differentiated regions along the anterior-posterior axis of the developing neural tube (**see Box 22B**)

B. molecular basis of neural induction

1. molecular interactions between cells (in early embryogenesis, between cells in adjacent germ layers) that are essential for shaping regional and cellular identity (**see Figure 22.5A**)

a. inductive signals are secreted by: notochord, floor plate, roof plate, somites, specific foci within the neuroectoderm (to name a few sources)

b. inductive signals are secreted and diffuse through extracellular spaces to act on adjacent tissues

2. examples:

a. steroid hormones: **retinoic acid** (RA) (**see Figure 22.5B**)

i. small, lipophilic molecule derived from vitamin A

ii. activates retinoid receptors, which are transcription factors that modulate the expression of target genes

iii. RA signaling drives cellular differentiation, regulating transitions between classes of neural stem cells

iv. *excess* or *insufficient* vitamin A (or retinoid-based medications) can disrupt early brain morphogenesis (**see Box 22C**)

b. peptide hormones: fibroblast growth factor, **bone morphogenetic proteins**, Wnt hormone family, and **sonic hedgehog**

i. bone morphogenetic proteins (BMPs) (**see Figure 22.5D**)

- BMPs are secreted by somites and surrounding mesodermal tissues
- and bind to receptor serine kinases that phosphorylate transcriptional regulators (SMADs), which in turn translocate to the nucleus and modulate gene expression
- induce the formation of bone cells in mesoderm (hence their name); but also they induce epidermis (skin) in ectodermal tissue …

- unless they are antagonized (by Noggin and Chordin), which then allows the ectoderm to differentiate into *neuroectoderm*
- evidently, *the CNS is "rescued" from becoming skin by antagonizing BMP activity!*

ii. sonic hedgehog (Shh) (**see Figure 22.5G**)

- important for neural tube closure
- important for establishing identity
- when present, it binds to surface receptors and promotes a switch from transcription repressors to transcription activators (Gli1-3) that modulate gene expression

3. inductive signaling provides a "transcriptional code" for establishing local identity in specific regions of the developing CNS, including the forebrain (**see Figure 22.6C-D**)

C. generation and differentiation of neurons and glia

1. in the adult brain, there are about *100 billion neurons* (and even more neuroglial cells)!
2. during the peak cell proliferation, the rate of neurogenesis is nearly *250,000 neurons per minute!*
3. **nearly all neurons are generated by the middle of the second trimester**; *thereafter, only very few neurons are ever generated in the CNS!* (consider the implications for learning and memory, motor skill acquisition, neuropathology and neural rehabilitation)
4. neuronal and glial genesis occurs in the **ventricular zone**
   a. precursor cells divide in the ventricular zone and produce other stem cells for many (symmetrical) mitotic cycles (**see Figure 22.7**)
   b. after asymmetrical division, one of the two daughter cells is destined to differentiate into a glial precursors and others into neuronal precursors, called **neuroblasts** (**see Figure 22.10**)
   c. postmitotic neuroblasts migrate away from the ventricular zone toward a target structure, such as the developing cerebral cortex, called the **cortical plate**, or remain closer to the ventricular zone to populate subcortical gray matter (primordial basal ganglia and diencephalon)
      i. many neurons in the CNS are guided to final destinations by (presumptive) glial cells that span the distance between the ventricular zone and the pia mater
         - for the developing cortical plate, neuroblasts migrate along **radial glial cells** (**see Figure 22.12-13**)

- when neuroblasts reach their final destination, they dissociate from radial glial processes and take up residence in a particular laminar or spatial position
- in the cortical plate, neuroblasts that will come to populate the deeper layers are generated first and migrate to the inner most laminae (**see Figure 22.8**)
- later, more superficial neuroblasts are generated and migrate through the deeper layers to reach the outer laminae of the developing cortical plate
- *the cortical plate develops in an "inside-out" pattern*
- thus, organized periods of neurogenesis are important for the development of region-specific cell types and axonal connections

ii. a number of congenital malformations are the result of migration errors; event subtle errors may lead to forms of mental retardation and cerebral palsy

iii. neuroblasts that differentiate into inhibitory interneurons are derived from the deep ganglionic eminence and migrate tangentially to reach their final destinations (**see Box 22F**)

D. how do precursor cells differentiate to produce the diverse forms of neurons and glia that are present in the mature CNS?

1. local cell-cell interactions mediated by cell surface receptors (who a cell's neighbors are), many of which are those same signals that served inductive signaling at some earlier stage in development (**see Figure 22.10**)
2. cell lineage—distinct histories of transcriptional regulation (who a cell's parent is)

E. after taking up residence in a target structure, a significant portion of the neurons produced (roughly half in certain CNS regions) undergo **apoptosis**

1. programmed cell death requiring the expression of so-called "suicide genes" whose products promote the dysfunction and dissolution of otherwise viable cells
2. cells that undergo apoptosis are not necessarily "less fit" (this does not seem to be a Darwinian-like developmental process)

F. in the third trimester and in early postnatal life, the neurons that survive elaborate dendritic arbors and send out axons (the story continues in the next few tutorials)

STUDY QUESTIONS

Q1. Which of the following statements about the **notochord** is MOST accurate?

A. The notochord is derived from the ectodermal germ layer.
B. Formation of the notochord is the principal developmental achieve of neurulation.
C. The notochord provides a migratory pathway for neural crest derivatives as they migrate toward their final locations in the developing embryo.
D. The notochord is an important source of inductive signals that induce the formation of the neural plate in the overlying ectoderm.
E. The spinal cord of the mature the nervous system is derived from the cells of the embryonic notochord.

Q2. What factor or factors account for the generation of diversity among the progeny of neuroblasts?

A. local cell-cell interactions mediated by cell surface receptors
B. the distinct histories of transcriptional regulation in the progeny
C. both cell-cell interactions and transcriptional history contribute to cellular diversity in the developing CNS