Neural Development

• In the developing nervous system there must be:
  – 1. The formation of different regions of the brain.
  – 2. The ability of a neuron to differentiate.
  – 3. The ability of axons to go to an appropriate location.
  – 4. The ability to set up synaptic circuits.
  – 5. The consolidation and maturation of neural connections.
Brain development

• Embryonic period
  – Rudimentary CNS structures established.
    • First 8 weeks of gestation

• Fetal development
  – Cortical, subcortical and fiber tract established
    • By birth major pathways complete

• Postnatal period
  – Robust connectivity
    • Trimmed back during development
Neuronal Differentiation

- Cells can be identified and traced.
- Can follow the cell as it divides and map the fate of its cell derivatives.
- In most species differentiation is dependent upon:
  - growth factor effects.
  - cell-cell interactions.
  - birthday of the cell.
Neuronal Differentiation

• Once a neural tube is formed neuroblasts must choose between becoming a glial cell and a neuron.
• There are several types of cells that can be formed.
• Often one glial cell type can influence the fate of other glial cells.
• For example, development of oligodendrocytes is in part regulated by type 1 fibrous astrocytes.
Neuronal Differentiation

- Neurotrophic factors are important for the survival of the neuron.
- Neurotrophic factors regulate the survival of neurons.
  - nerve growth factor
  - brain-derived neurotrophic factor
  - neurotrophin-3
- Different factors support different neurons.
Neurotrophic factors

Transforming growth factor-Beta (TGF-β) family

- Glial derived neurotrophic factor (GDNF)
- TGF-β1, 2, and 3
- Bone morphogenetic proteins

Neurotrophins

- NGF
- BDNF
- NT-3
- NT-4/5
- NT-6

Other trophic factors

- Ciliary neuronotrophic factor (CNTF)
- Epidermal growth factor (EGF)
- Leukemia inhibitory factor
- Insulin and Insulin-like growth factors
- Fibroblast growth factors

This list is not for memorization
Neuronal Differentiation

• Actually, combinations of growth factors will support neuronal survival.
• For example, ciliary ganglion neurons depend on FGF, laminin, and depolarization for survival.
• These agents function by preventing the neurons from carrying out a program of cell death that would be constitutively expressed in the absence of these factors.
Studies on neural crest cells have shown that the local environment can also play a role in the type of transmitter that a neuron synthesizes.

Sympathetic neurons grown in isolation synthesize norepinephrine as the transmitter.

These neurons grown in conditioned medium can be induced to synthesize acetylcholine.
Neural Crest Gene Regulatory Network
• Often the **position of a neuron** is important in determining the type of neuron that will develop.

• In the Drosophila eye there are specific cells that are specialized receptor neurons called R1 - R8.
Neuronal Differentiation

- Often the **position of a neuron** is important in determining the type of neuron that will develop.
Neuronal Differentiation

- R7 has a receptor encoded by the *sevenless* gene.

- Without *sevenless* the R7 cell will not develop.
Neuronal Differentiation

- R8 has the *boss* gene.

- Without *boss*, the R7 cell will not develop because the *boss* protein is the ligand for the receptor that is on the R7 cell.
Neuronal Differentiation

- Neurons in the cerebellum migrate over glial cells.
- Cell migration in cerebellum is important.
- In weaver mice the granule cells of the cerebellum can not reach their proper location.
- The cause is a defect in the granule cells of weaver mice that prevents them from interacting with the glial cells.
Neuronal Differentiation

• The type of cell that develops is related to the ‘birthday’ of the cell.
• ‘Birthday’ is the day the neuron stops dividing and a post-mitotic neuron develops.
• Early neurons develop into the deeper cortical layers.
• Later neurons develop into the more superficial cortical layers.
Neuronal Differentiation

- In the cortex the neurons of the superficial layer must migrate past the deeper neurons.
- The commitment occurs just prior to the cessation of cell division.
- The commitment is more important in the cortex that the route of migration.
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Axonal Guidance

• Retinal ganglion cells
  • Some cross
  • Others go to cortex on same side.
• How do they know?
Axonal Guidance

- Two major molecules involved:
  - Cell Surface molecules
  - Extracellular matrix molecules
Axonal Guidance

- Integrins on axon growth cones interact with:
  - Laminin
  - Fibronectin
- Cadherins
  - Expressed on growth cones and on
  - Cells which they come in contact with
Axonal Guidance

• Cell Adhesion molecules
  • Ng-CAM: promotes elongation of axons along astrocytes and Schwann cells in both the CNS and PNS.
  • N-CAM: allow neurons to attach to each other. They can form nerve bundles.
Axonal Guidance

• Chemotropic factors
  • Netrins

• Negative regulation of axonal growth
  • IN-1 inhibits axon growth
  • Semaphorins: chemorepellant
Figure 22.11  Radial migration in the developing cortex. (A) Section through the developing forebrain showing radial glial processes from the ventricular to the surfaces. Micrograph shows migrating neurons labeled with an antibody to neuregulin, specific for migrating cortical neurons. (B) Enlargement of boxed area in (A). Migrating neurons are intimately apposed to radial glial cells, which guide them to their final position in the cortex. Some cells take a nonradial migratory route, which can lead to wide dispersion of neurons derived from the same precursor. (C) A single neuroblast migrates upon a radial glial process (based on serial reconstruction of EM sections as well as in vitro assays of migration, as shown in the accompanying micrograph). Cell adhesion molecules found on the surface of either the neuron (green) or the radial glial process (tan) are indicated in the respective boxes. (After Rakic, 1974; micrographs courtesy of E. S. Anton and P. Rakic.)
Kallman Syndrome

• Anosmia
• Infertility
• Olfactory placode gives rise to:
  – Olfactory receptor neurons
    • Receptors in olfactory epithelium process to the olfactory bulb.
  – GnRH cells
    • Located in the preoptic and suprachiasmatic nuclei of the anterior hypothalamus.
Both migrate toward through the cribiform plate of the ethmoid bone.

Olfactory neuron processes migrate rostrally to the olfactory bulb.

GnRH neurons migrate caudally to the diencephalon.

In Kallmann’s syndrome neither migrate through the cribiform plate and don’t reach the brain.
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Trophic Interactions

- As synapse is made it is dependent on the target for survival and differentiation.
- This is a trophic interaction
- Neurotrophic factors maintain the axon
- Apoptosis or cell death occurs if the trophic factors are not present
- More neurons are made than survive.
Trophic Interactions

• It is important to consider that during development of the nervous system 1/2 of the neurons may die during development.

• In the cat retina, 80% of the retinal ganglion cells die. However, this is species specific and only 40% die in the chick retina.
Trophic Interactions

- In the chick removal of the limb bud results in fewer anterior horn cells.
- Transplanting extra limb bud leads to neurons remaining and not dying.
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Critical Periods

• Normally the nervous system requires additional sensory activity to refine neuronal connections.
• There are CRITICAL PERIODS OF DEVELOPMENT.
• These periods are times when the wiring of the brain becomes refined as a result of interactions between the organism and the environment.
A critical period of development exists if:

• Lack of a stimulus during the critical period results in long-lasting/permanent sensory deficits.

• Exposure to the normal stimulus during ONLY the critical period results in normal sensory development.
• Visual system
  – Visual deprivation during the postnatal period causes abnormalities in the retina and visual pathway nuclei.

• Auditory system
  – Sound deprivation during a critical period in the development results in both anatomic and behavioral changes in the auditory system.

• Vestibular system
  – NASA experiments have shown that there is a critical period of development of the vestibular system.
Critical Periods

• Studies in the 1940 demonstrated that infants raised in an environment with sensory deprivation developed social and behavioral problems.
• Monkeys that are isolated for six months after birth develop severe alterations in behavior.
Critical Periods

- Different regions of the brain have different times which are critical for development.
- Clinically this is important.
Critical Periods

- There is a critical period during the development of language
- Persistent auditory deprivation can lead to deficits in language acquisition
- Recurrent middle ear infections – language problems.
A critical period for learning language is shown by the decline in language ability (fluency) of non-native speakers of English as a function of their age upon arrival in the United States. The ability to score well on tests of English grammar and vocabulary declines from approximately age 7 onward. (After Johnson and Newport, 1989.)
These postnatal critical periods include:

- emotional control, ages 0-2;
- vision, ages 0-4;
- social attachment, ages 0-2;
- vocabulary, ages 0-3;
- second language, ages 0-10;
- math/logic, ages 1-4;
- music, ages 3-10
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