Medical Neuroscience | Tutorial Notes

Construction of Neural Circuits

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 structure and function of growth cones.
2. Discuss the major classes of molecular signals that guide axonal growth.
3. Discuss the mechanisms of neurotrophin signaling.

TUTORIAL OUTLINE

I. Introduction

- A. mechanisms of neural development
  1. **genetic specification**: phenotypes produced by spatial and temporal patterns of gene expression in cells derived from common precursors
  2. **self-organization**: phenotypes produced by cell-cell interactions mediated by endogenous patterns of activity in neural networks
  3. **sensorimotor experience**: the modulation of endogenous neural activity by the activation of sensory receptors during environmental interactions
- B. each of these basic mechanisms is subject to modification due to the consequences of genetic mutation, disease, exposure to environmental and dietary toxins, and normal and abnormal sensorimotor experience

II. **Genetic specification** and **self-organization** in early brain development: axon outgrowth and path-finding through the developing nervous system

- A. molecular mechanisms establish polarity in differentiating neuroblasts

[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. neurites (undifferentiated processes) extend from the cell bodies
2. a single process becomes the presumptive axon (from the apical domain of the cell)
3. other neurites (emanating from basal domain) become dendrites

B. growing (presumptive) axons explore their environment (i.e., the extracellular matrix) with a specialized structure at the distal tip of the axon, called a **growth cone** (see **Figure 23.2 & 23.3**[2])

1. contains abundant mitochondria (to fuel their high metabolic needs), thin actin filaments and microtubules (to allow for changes in shape), and smooth endoplasmic reticulum (to produce large quantities of plasma membrane)
2. extend cellular processes, called lamellipodia (flat sheet-like processes) and filopodia (elongated, finger-like processes), that sample the local environment
3. these processes rapidly appear and disappear at the leading edge of the growth cone, as the structure responds to local cues
    a. receptors and channels (TRP) on the surface of the filopodia and lamellipodia transduce local signals from adhesion molecules in the extracellular matrix and soluble molecules that diffuse through the extracellular spaces (see below)
    b. calcium is a key mediator of these signals modifying actin filament and microtubule dynamics within growth cones
4. the entire growth cone is highly motile; in response to local signals, growth cones may change their speed or direction of growth
5. at "forks in the road", growth cones must sample the local environment and respond with directed growth (e.g., see **Boxes 23A** & **23B**)

C. as growth cones traverse the neural terrain of the developing nervous system, axons grow in length by adding membrane both proximally (i.e., from the cell body end of the axon) and distally (i.e., from the growth cone), a process called **elongation**

STUDY QUESTION

Q1. Which of the following projections must confront a "fork in the road" in development at which growth cones must choose to cross the midline of the developing CNS?

A. the central axons of first-order spinal mechanosensory afferents in the spinal cord
B. the central axons of first-order trigeminal pain and temperature afferents in the brainstem
C. spinothalamic tract axons in the ventral white commissure of the spinal cord
D. optic radiation axons in Meyer's loop
E. axons grown from neurons in Clarke's nucleus that are pioneering the dorsal spinocerebellar tract

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

D. molecular signals for axon guidance

1. **cell-associated molecules** on the surface of cells and molecules embedded within the extracellular matrix (see **Figure 23.4**)

a. general mode of operation:

(i) molecules on the surface of growth cones and axons interact with similar (or in some instances, the same) molecules on other cellular surfaces, and with molecules embedded in the extracellular matrix

(ii) such molecular interactions trigger cascades of intracellular events within the growth cone that lead to axon elongation

(iii) some of these molecules (ephrins and Eph receptors) are important for topographic map formation, as they signal appropriate substrata for axonal growth and synaptogenesis (see **Figure 23.7**)

b. certain classes of molecules mediate interactions that stabilize the linkages between axons and glial cells and between adjacent axonal membranes, thus permitting the establishment of axonal tracts (fasciculation or bundling of axons)

2. diffusible molecules

a. general mode of operation:

(i) target tissues secrete soluble molecules that diffuse into the extracellular fluids and effect axonal growth and survival

(ii) such molecules interact with receptors on the surface of the growth cones and trigger cascades of intracellular events that mediate these effects

b. **tropic molecules**: guide growing axons toward or away from a source (see **Figure 23.5** & **23.6**)

(i) chemo-attractant

(ii) chemo-repellant

c. **trophic (neurotrophic) molecules**

(i) promote the survival and growth of neurons and their processes (axons and dendrites)

(ii) match innervation (numbers of efferent and afferent neurons) with the amount of target tissue that is present in the periphery (see **Figure 23.10**)

(iii) establish the appropriate degree of convergence and divergence between neurons and their targets (see **Figure 23.11** & **23.12**)

(iv) shapes the distribution of local neuronal processes (**Box 23D**)

(v) the production of neurotrophins by target tissues is regulated by patterns of neural activity

- provides the basis for **activity-dependent competition** among a set of inputs that are seeking to establish connections with the same target cell
- blocking activity in the pre- or post-synaptic element disrupts competitive interactions

(vi) important (known) trophic factors (**neurotrophins**) (see **Figure 23.16**)

- **nerve growth factor** (NGF)
- **brain-derived neurotrophic factor** (BDNF)
- neurotrophin-3 (NT3)
- neurotrophin-4/5 (NT4/5)

(viii) neurotrophin signaling

- the selective actions of the neurotrophins arise from interactions with different classes of surface-bound receptors: **Trk receptors** and the **p75 receptor**
- Trk receptors (three types)
  - all single, transmembrane proteins with tyrosine kinase (trk) activity on their cytoplasmic domain
  - certain neurotrophins bind to certain types of Trk-receptors (see **Figure 23.16**)
- p75 receptor
  - all known neurotrophins bind to p75
  - but affinity is highest for the unprocessed, newly secreted form of neurotrophin
- neurotrophin receptors can activate a variety of second messenger systems within target cells mediating both local effects within a process and transcription-dependent effects in the cell body (see **Figure 23.17**)
- neurotrophin signaling is implicated in a variety of degenerative diseases of the CNS

E. synapse formation

1. begins with recognition of presumptive pre- and post-synaptic elements by calcium-dependent cell adhesion molecules (see **Figure 23.8A**)

2. once initial specialization is established, additional adhesion molecules from the family of calcium-independent cell adhesion molecules, together with the activity of ephrin ligands and their Eph receptors, induce the assembly of presynaptic machinery for chemical neurotransmission and postsynaptic specialization necessary to insert specific receptors and transduce chemical signals (see **Figure 23.8B-C**)

    a. neurexin acts to assemble the active zone in the presynaptic membrane

    b. the presynaptic terminal releases neuregulin, which influences the organization of the postsynaptic site

    c. neuroligin acts to assemble postsynaptic density proteins that anchor the transduction machinery

STUDY QUESTION

Q2. Which of the following functions is attributable to the activity of neurotrophins?

A. attract the growth of elongating axons to a certain region of the developing CNS or PNS
B. repel the growth of elongating axons to a certain region of the developing CNS or PNS
C. promote the survival and growth of neurons and their processes
D. match neural innervation with the amount of target tissue
E. establish the appropriate degree of convergence/divergence between neurons and their targets
F. A & B are both important functions of neurotrophins
G. C, D & E are all important function of neurotrophins