Medical Neuroscience | Tutorial Notes

Synaptic Plasticity: LTP & LTD

Map to Neuroscience Core Concepts[1]

NCC2. Neurons communicate using both electrical and chemical signals.

NCC4. Life experiences change the nervous system.

NCC8. Fundamental discoveries promote healthy living and treatment of disease.

Learning Objectives

After study of today's tutorial, the learner will:

1. Characterize general cellular mechanisms for synaptic change.
2. Characterize long-term potentiation (LTP).
3. Discuss the role of AMPA and NMDA subtypes of glutamate receptors in the induction and maintenance of LTP.
4. Characterize long-term depression (LTD).
5. Discuss the molecular basis of LTD in the cerebral cortex and cerebellar cortex.

Tutorial Outline

I. Introduction

- A. **plasticity**: the capacity of the nervous system to change
- B. plasticity occurs at all levels of organization (i.e., synapses, neural circuits, neural systems)
- C. plasticity is the basis of all neural functions that involve change (e.g., memory, acquisition of motor skill or cognitive skills, adaptation to and recovery from injury or disability)

II. Overview of long-term synaptic plasticity

- A. changes in synaptic function that occur over a very long time frame: hours, days, months (and maybe years)
- B. changes in synaptic function are the cellular correlates of learning and memory
- C. general cellular mechanisms for synaptic change:
  1. neural activity triggers the activation of postsynaptic, second messenger systems
  2. the trigger is usually a specific alteration in the levels of intracellular calcium in the postsynaptic neuron

[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.

3. Ca-dependent second messenger systems alter the activity of protein kinases (phosphorylate target proteins) and phosphatases (dephosphorylate target proteins)
4. alterations in protein phosphorylation mediate the early stages of long-term synaptic plasticity (changes in phosphorylation induce changes in protein function)
5. the more long-lasting changes in synaptic strength are brought about by alterations in gene transcription induced by second messenger systems

III. **long-term potentiation** (LTP)

A. a long lasting *INCREASE* in postsynaptic currents induced by brief, *high-frequency* stimulation of an afferent pathway (see **Figure 8.7**[2])

B. characteristics

1. *the postsynaptic neuron must depolarize*
   a. induction of LTP requires pairing of presynaptic activity *AND* postsynaptic depolarization (satisfies Hebb's postulate)
   b. mediated by NMDA receptors (see below)
2. *LTP only occurs at active synapses* (see **Figures 8.7-8.9**)
3. *other inputs that are concurrently active, even weakly active, may become potentiated* (see **Figure 8.9**)
   a. this allows for the selective enhancement of two distinct inputs onto the same postsynaptic neuron
   b. provides for the basis of associative learning (classical conditioning)
4. persists for at least many weeks
5. studied primarily in the hippocampus, but basic phenomenon is assumed to occur throughout the cerebral cortex (and subcortical circuits)

C. molecular basis of LTP

1. **induction** of LTP requires activation of **NMDA** (*N*-methyl-D-aspartate) subtype of ionotropic glutamate receptor
   a. blockade of NMDA receptors has little effect on synaptic responses elicited by low-frequency stimulation of an afferent pathway
   b. however, blockade of NMDA receptors prevents the development of LTP during high-frequency stimulation
2. two factors explain the necessity of NMDA receptors for the induction of LTP (see **Figure 8.10**):
   a. voltage-dependency of NMDA receptor mediated currents
      i. near resting membrane potentials, the channel pore is blocked by magnesium ions (Mg^{++})
      ii. with significant depolarization, Mg^{++} is expelled from the channel pore and current is allowed to pass
   b. permeability of NMDA channels to calcium

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

i. influx of calcium triggers a series of second messenger systems that mediate the **maintenance** of LTP, especially calcium-dependent protein kinases (see **Figure 8.13**)

ii. changes in the postsynaptic neuron involve the addition of new ionotropic glutamate receptors (AMPA receptors) that enhance the postsynaptic response

iii. such changes may "awaken" "silent synapses" (see **Box 8B**)

iv. in addition, new spine structures on dendrites (sites of postsynaptic contact) may form (see **Figure 8.12** & **8.15**)

v. changes may also involve the presynaptic terminal (e.g., increased probability of exocytosis or increased amount of glutamate released per vesicle)

3. Review the contributions of AMPA and NMDA receptors to LTP by viewing an online animation that accompanies *Neuroscience, 5th. Ed.*, Chapter 8: **Animation 8.2 AMPA and NMDA Receptors** [click here]

4. consider the study question at the end of this tutorial

IV. **long-term depression** (LTD)

A. a long lasting *DECREASE* in postsynaptic currents induced by relatively prolonged, *low-frequency* stimulation of an afferent pathway

B. LTD in the **cortex** (see **Figure 8.16**)

1. characteristics

a. induction of LTD requires pairing of presynaptic activity and postsynaptic depolarization

b. phenomenon persists for at least many weeks

2. molecular basis of LTD

a. induction of LTD requires activation of NMDA receptors and entrance of calcium into postsynaptic neuron

b. LTD in cortical neurons is induced when calcium levels are **low**

i. remember, a large influx of calcium triggers LTP …

ii. … but a small influx triggers LTD by activation of calcium-dependent protein phosphatases

C. LTD in the **cerebellum** (see **Figure 8.17**)

1. induction of LTD requires pairing of parallel fiber (cerebellar granule cell) and climbing fiber activity (climbing fibers provide the 'learning signal'; these inputs originate in the inferior olivary nucleus in the medulla)

2. phenomenon persists for at least many weeks

3. molecular basis of LTD in the cerebellum is different from what occurs in cerebral cortex

a. induction requires activation of metabotropic glutamate receptors (rather than NMDA receptors)

b. activation also requires activation of climbing fibers, which depolarize the membrane, open voltage-gated calcium channels and ensure a rapid influx of Ca

c. second messenger systems regulated by the metabotropic glutamate receptors also lead to an increase in intracellular Ca

d. activated PKC (protein kinase C) phosphorylate AMPA receptors in the cytoplasm, which leads to their internalization from the postsynaptic membrane

e. thus, in the cerebellum (but not the cerebral cortex!), elevated intracellular Ca leads to LTD

STUDY QUESTION

Why are **NMDA glutamate receptors** so important for synaptic plasticity?

A. because the conductance of the channel is voltage-dependent due to the binding of magnesium to a site on the pore-loop
B. because the channel is permeable to calcium ions
C. because NMDA receptors activate G-proteins on the cytoplasmic surface of the receptor complex
D. A & B are both especially important
E. A, B & C are all especially important