Medical Neuroscience | Tutorial Notes

Neurotransmitter Receptors

MAP TO NEUROSCIENCE CORE CONCEPTS[1]

NCC2. Neurons communicate using both electrical and chemical signals.

LEARNING OBJECTIVES

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

1. Discuss the means by which ligand-gated ion channels affect the membrane potential of postsynaptic neurons.
2. Compare and contrast the structure and function of ligand-gated ion channels and metabotropic (G-protein coupled) receptors.
3. Discuss the properties of the NMDA receptor for glutamate and why it is important for synaptic plasticity.
4. Account for the factors that determine the effect of neurotransmitters on postsynaptic neurons.

TUTORIAL OUTLINE

I. Overview of neurotransmitters
   - A. review mechanisms of chemical synaptic neurotransmission (see **Figure 5.3**[2])
   - B. two broad classes based on molecular size and chemical class (see **Figure 6.1**)

II. Ionotropic receptor (ligand-gated ion channel) activation
   - A. overview
     1. the *same* molecular complex binds the neurotransmitter and forms a channel for the passage of ions across the plasma membrane (see **Figure 5.16A**)
     2. mediate most rapid post synaptic effects (typically, in millisecond range)
     3. remember, *the response elicited by any given neurotransmitter will depend upon the postsynaptic receptor and the associated types of channels and second messenger systems that may be activated*
   - B. general molecular structure (see **Figure 6.3A**)
     1. comprised of four or five subunits

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

2. each subunit has
    a. extracellular N-terminal domain that contains the neurotransmitter receptor
    b. membrane spanning domain that forms the ion channel
    c. intracellular domain, where other molecules may interact to modulate channel function
3. different subunits may be combined to produce functional diversity for any given type of channel (see **Figure 6.3F**)

C. important examples include:
1. nicotinic acetylcholine receptors (see **Figures 6.3**)
2. AMPA & NMDA receptors for glutamate (see **Figures 6.6** & **6.7**)
3. $GABA_A$ receptors (see **Figures 6.9**)

D. postsynaptic currents induced by ligand binding to ionotropic receptors
1. channels are gated by binding of neurotransmitter to receptor site (in contrast to voltage-gated ion channels)
2. net current flows through channel pores if:
    a. **channel conductance (g) > 0**, which happens rapidly when neurotransmitters bind
    b. **there is a driving force** for current flow; or in mathematical terms, when $V_m - E_{rev} \neq 0$ (the driving force can be positive or negative)
3. Ohm's law for ligand-gated ion channels:

$$PSC = g_{ligand} (V_m - E_{rev})$$

PSC	postsynaptic current induced by ligand binding
g_{ligand}	conductance gated by ligand binding
V_m	membrane potential when ligand binds
E_{rev}	reversal potential of the ligand-gated conductance

4. consider the nicotinic acetylcholine receptor at the neuromuscular junction (see **Figure 5.17** & **6.3**)
    a. the channel is gated by the binding of acetylcholine released by the terminals of motor neurons in the brainstem and spinal cord
    b. the channel pore is relatively non-selective (much less selective than typical voltage-gated ion channels); most univalent cations can pass (e.g., sodium, potassium)
    c. in most muscle fibers, E_{rev} is near 0 mV
    d. postsynaptic current, called the endplate current (EPC), is a product of *conductance* (binding of acetylcholine) and *driving force* (membrane potential relative to the reversal potential)

e. consider the **Study Questions** at the end of these tutorial notes

E. consider the behavior of an unusual, but critically important ligand-gated ion channel for glutamate: the **NMDA receptor** (see **Figure 6.6**)

1. channel pore is gated by the binding of glutamate, but also requires the presence of a "co-agonist", the amino acid glycine

2. channel pore contains a binding site for magnesium (Mg^{++})

a. when the postsynaptic neuron is at resting membrane potentials, extracellular Mg^{++} is attracted to the channel pore (by electrostatic forces) and effectively blocks the pore

b. when the postsynaptic neuron is depolarized, extracellular Mg^{++} is repelled from the channel pore (again, by electrostatic forces) and the pore is unblocked

c. thus, the channel is gated by glutamate, but the conductance is voltage-dependent

3. channel pore is relatively non-selective for cations (Na^{+}, K^{+}, Ca^{++})

a. the entrance of is Ca^{++} significant, since Ca^{++} is a key second-messenger within the cytoplasm mediating a variety of effects that can impact the structure and function of postsynaptic neurons

b. the amount of Ca^{++} that enters a postsynaptic process when NMDA receptors are activated and the postsynaptic neuron is depolarized is a critical factor in synaptic plasticity (much more on this in Friday's session)

III. Metabotropic receptors

A. termed **metabotropic**, because the eventual passage of ions through a channel requires one or more metabolic steps (see **Figure 5.16B** & **6.4**)

1. receptor and ion channel are *separate* molecules in the membrane

2. receptor interacts with the ion channel indirectly via the activity of a set of **G-proteins** (thus, called "G-protein-coupled receptors")

3. typically, energized G-proteins in turn activate an effector enzyme, which produces a second messenger (see **Figures 7.5** & **7.6**)

a. effector enzymes produce a variety of second messenger systems each of which may have distinct effects

b. by this means, the triggering molecular signal (i.e., a neurotransmitter) is greatly amplified (one signal $\Rightarrow$ many second messengers) and diversified (one signal $\Rightarrow$ many intracellular effects) (see **Figure 7.2**)

4. mediate slower developing and more persistent post synaptic effects than the ionotropic receptors

a. onset of post synaptic potential within a few to 10s of milliseconds of the presynaptic action potential

b. post synaptic potential may last for 100s of milliseconds or longer

c. certain second messenger systems may affect gene transcription and thereby produce post synaptic effects that last many days (see **Figure 7.11**)

B. general molecular structure

1. receptor molecule is a monomeric protein (see **Figure 6.4A**)

a. extracellular domain, including the N-terminus

b. seven membrane spanning domains that form the binding site for the neurotransmitter (common to all G-protein-coupled integral membrane proteins)

i. stay tuned! this family of G-protein coupled proteins show up in surprising places (besides postsynaptic membranes):

- the detection of odors is based upon the activity of one member of this family of proteins
- another member of this family mediates the conversion of photons into electrical signals in photoreceptors

ii. intracellular domain, which contains portions of the C-terminus and membrane spanning domains that bind the G -proteins

C. important examples of metabotropic receptors include: muscarinic acetylcholine receptors, metabotropic glutamate receptors, and α & β adrenergic receptors

IV. remember, *the response elicited by any given neurotransmitter will depend upon the post synaptic receptor and the associated types of channels and second messenger systems*

STUDY QUESTIONS

1. What is the EPC when acetylcholine binds and the muscle fiber is clamped at -100 mV? (remember that an inward current is carried by positive charge flowing into the cell)

A. large inward current
B. small inward current
C. no net current
D. small outward current
E. large outward current

2. What is the EPC when acetylcholine binds and the muscle fiber is clamped at -20 mV?

A. large inward current
B. small inward current
C. no net current
D. small outward current
E. large outward current

3. What is the EPC when acetylcholine binds and the muscle fiber is clamped at 0 mV?

    A. large inward current
    B. small inward current
    C. no net current
    D. small outward current
    E. large outward current

4. What is the EPC when acetylcholine binds and the muscle fiber is clamped at +20 mV?

    A. large inward current
    B. small inward current
    C. no net current
    D. small outward current
    E. large outward current

5. What is the EPC when acetylcholine binds and the muscle fiber is clamped at +70 mV?

    A. large inward current
    B. small inward current
    C. no net current
    D. small outward current
    E. large outward current

one final question to consider:

6. What explains the value of E_{rev} at the motor endplate?

    A. E_{rev} is the membrane potential that drives Na^+ into the cell, but precisely opposes the outflow of K^+
    B. E_{rev} is the membrane potential that drives K^+ out of the cell, but precisely opposes the influx of Na^+
    C. E_{rev} is the membrane potential at which there is no net flow of current