# Medical Neuroscience | Tutorial Notes

## Synaptic Transmission

### *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. Compare and contrast the structural and functional similarities and differences between electrical and chemical synapses.
2. Describe the sequence of events responsible for the transmission of a neural impulse from one neuron to the next via a chemical synapse.
3. Characterize the critical role of calcium in chemical neurotransmission.
4. Discuss the mechanisms of action by which Botox affects neurotransmission.

### *TUTORIAL OUTLINE*

I. Introduction

- A. Two types of synapses:
  1. **electrical synapses** (gap junctions): permits passive current flow through open pores that interconnect adjacent neurons
  2. **chemical synapses**: enable intercellular communication via the secretion of chemical messengers that must diffuse the gap between adjacent neurons

II. General comparison of electrical and chemical synapses (summarized in **Table** at end of handout; also see **Figure 5.1**[2])

III. A closer look at chemical synapses (see **Figure 5.3**)

- A. sequence of events involved in chemical neurotransmission

  [note: the numbered items below correspond to the numbers in **Figure 5.3**]

  1. the presynaptic terminal contains:
     - a. neurotransmitter that is synthesized and stored in synaptic vesicles
     - b. a pool of vesicles that are "docked" along an active zone in the presynaptic membrane, poised to fuse with the plasma membrane

[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. an action potential invades the presynaptic terminal
3. associated change in membrane potential causes the opening of voltage-gated $Ca^{++}$ channels
4. because of the steep concentration gradient for $Ca^{++}$ across the plasma membrane, **$Ca^{++}$ rushes into the presynaptic terminal**
5. via a cascade of molecular events, $Ca^{++}$ causes the fusion of "docked" vesicles with the presynaptic plasma membrane along the synaptic cleft
6. vesicle fusion releases neurotransmitter into the synaptic cleft
7. neurotransmitter diffuses across the synaptic cleft and binds specific receptors in the post synaptic membrane
8. binding of neurotransmitter causes the opening or closing of ion channels in the postsynaptic membrane
9. current flows through open channels in the postsynaptic membrane or that membrane becomes less "leaky" due to closure of certain channels; consequently, the postsynaptic membrane becomes either depolarized or hyperpolarized
    a. if positive current flows (i.e., cations in) and the membrane is depolarized, voltage-gated $Na^{+}$ channels will open and a postsynaptic potential will be generated; if threshold is reached, the postsynaptic neuron will then fire an action potential
    b. if negative current flows (i.e., anions in or cations out), then the membrane will be hyperpolarized and the postsynaptic membrane will be further from threshold and less likely to fire an action potential
    c. meanwhile, neurotransmitter is removed by glial or presynaptic uptake, or by enzymatic degradation
10. vesicular membrane is retrieved from presynaptic membrane (see **Figure 5.9**)

B. critical role of calcium in vesicle fusion

1. depolarization of the presynaptic membrane opens voltage-gated $Ca^{++}$ channels (see **Figure 5.10**)
2. influx of $Ca^{++}$ is both necessary and sufficient for vesicle fusion and neurotransmitter release (see **Figure 5.11**)
    a. fusion requires the coordinated interactions of dozens of molecules in the vesicular membrane, presynaptic cytosol and presynaptic terminal membrane (see **Figure 5.13**)
    b. influx of $Ca^{++}$ is the trigger that orchestrates these interactions, by binding first to a vesicular membrane protein, **synaptotagmin**
    c. a complex of proteins (SNARE complex) are then activated to accomplish the fusion of docked vesicles (see **Figure 5.14A, B**)
    d. other proteins (see **Figure 5.13**) are involved in:

(i) the "docking" and "priming" process

(ii) the formation of a "fusion pore"

(iii) the incorporation of vesicular membrane into presynaptic terminal membrane

(iv) the recycling of vesicular membrane (see **Figure 5.15**)

e. several of these proteins are the targets of natural toxins produced by certain bacteria, plants and animals (see **Boxes 5B & 5C**)

(i) clostridial toxins produced by certain types of bacteria are responsible for diseases, such as botulism and tetanus

(ii) many toxins are proteases that disrupt the SNARE complex

- some cleave the synaptic vesicle protein, synaptobrevin
- others cleave syntaxin or SNAP-25

(iii) cleavage of important synaptic vesicle proteins renders the synapse incapable of vesicle fusion and therefore, incapable of neurotransmission

(iv) Clinical application: "Botox" is a commercial formulation of the botulinum toxin that is especially useful clinically to treat spasticity and other forms of involuntary muscle fasciculation and twitching

C. let's summarize the processes by which chemical synapses operate by viewing a short online animation that accompanies *Neuroscience, 5th. Ed.*, Chapter 5: **Animation 5.1 Synaptic Transmission** [click here]

## *STUDY QUESTION*

The SNARE complex forms as proteins bound to the vesicle membrane interact with proteins bound to the presynaptic terminal. What is the function of the **SNARE complex**?

A. The SNARE complex facilitate the formation of a fusion pore between the vesicle membrane and the presynaptic terminal membrane.

B. The SNARE complex functions to snare free neurotransmitter that diffuses into the synaptic cleft.

C. The SNARE complex functions to facilitate the retrieval of vesicle membrane from the presynaptic membrane after release of neurotransmitter.

D. The SNARE complex functions to facilitate the loading of presynaptic vesicles with neurotransmitter.

E. The SNARE complex functions to snare recycled vesicles and deliver them to endosomes in the presynaptic terminal.

Table. Summary of electrical and chemical synapses in the CNS.

| Electrical Synapses | Chemical Synapses |
|---|---|
| *General function* | |
| **Very rapid communication or synchronization of a small pool of nearby neurons** | **Major means of communication between neurons; provides basis of neural plasticity** |
| Allows for passage of small, non-current carrying molecules (e.g., ATP, second messengers) | Molecules do not pass from the cytoplasm of one cell to another |
| *Prevalence* | |
| Abundant in developing nervous system | Rare and/or very immature in developing nervous system |
| Relatively rare in mature nervous system | Principal type of synapse in mature nervous system |
| *Morphology* | |
| Plasma membranes of communicating cells are closely apposed | Plasma membranes are close, but separated by a distinct **synaptic cleft** |
| Formed by the alignment of **connexons**, also called **gap junctions**, which are made from integral membrane proteins in both plasma membranes that form channels for the passage of small molecules (see Figure 5.2) | Synaptic cleft; no connexons |
| No synaptic vesicles or neurotransmitter molecules | **Synaptic vesicles** contain **neurotransmitter** molecules |
| No post synaptic receptors | **Neurotransmitter-specific receptors** (i.e., ligand-gated receptors) in post synaptic plasma membrane |
| Usually occur between neuronal cell bodies (somatic) or dendrites (dendro-dendritic) | May be axo-dendritic, axo-somatic, axo-axonal (and dendro-dendritic) |
| *Physiology* | |
| Current flows by direct diffusion of ions from one cell to another; also other important small molecules (e.g., ATP, cAMP, $Ca^{++}$) may pass | Current does not flow directly from one cell to another; post synaptic current develops secondarily to binding of neurotransmitter to its receptor and the opening/closing of channels |
| Very rapid communication; synaptic delay < 0.1 msec | Rapid communication, but slower than electrical synapses; synaptic delay ~ 0.5 msec |
| Communication may be bi-directional | Communication is only uni-directional |
| Probability of transmission (= presynaptic action potential followed by postsynaptic potential) is very high (~100%) | Probability of transmission is more variable (~20-90%) |