Introduction to Synaptic Transmission.

In the nervous system the action potential is normally initiated as a result of a depolarization occurring at excitatory synapses. There are also inhibitory synapses which can reduce the effectiveness of excitatory synapses. There are 2 varieties of synaptic transmission, chemical and electrical. The electrical form uses ionic channels (called connexins) that traverse both presynaptic (input) and postsynaptic (output) membranes. Depolarising currents due to presynaptic spikes are injected directly into the postsynaptic cell through these channels, almost as though there were no synaptic gap. However, electrical synapses are rare, have very specialized roles, and will not be considered further here. Chemical synapses release neurotransmitters which act on the postsynaptic cell, via specialized membrane proteins called receptors. For many years it was thought that chemical transmission would be too slow to explain the rapidity of synaptic action. But although like all small molecules neurotransmitters diffuse rather slowly (diffusion constant about 1 $\mu m^2\ msec^{-1}$), the synaptic gap is so short (about 50 nm) that it is not a major delay.

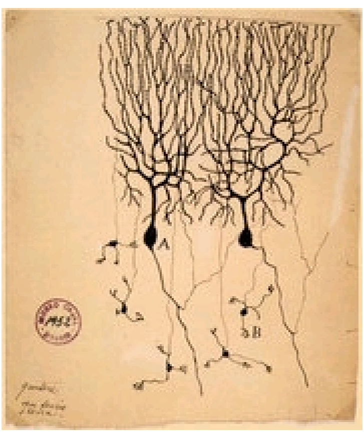
[Note: when a substance diffuses its molecules undergo a random walk in space, so it gradually spreads out. Because the molecules move randomly, the highest concentration will always be at the point of origin, but the point where the concentration has fallen to half the highest concentration (i.e. the position of the advancing concentration "wave") does not advance linearly with time, but as the square root of time. This accounts for the units of the diffusion constant.]

There are 2 major types of chemical synaptic action: fast and slow (though often both types are found at the same synapse). These differences reflect a fundamental division of the type of postsynaptic receptor involved. The 2 basic classes of receptor are ionotropic receptors (typically rapidly-acting) and metabotropic receptors (typically slower in action).

Ionotropic receptors function both as binding sites for neurotransmitters and as ion channels. Although they function as ion channels, they are referred to as receptors. Thus the voltage-dependent sodium channel, often called just a sodium channel, has a pore that selectively allows sodium permeation, but is gated by membrane potential. The nicotinic acetylcholine receptor binds the neurotransmitter acetylcholine, but the pore is not selective for acetylcholine (even though acetylcholine is an ion) – it lets through both sodium and potassium (see next lecture). The nAChR is gated by the binding of ACh. It is important to realize that these protein molecules have dual functions: as receptors for neurotransmitters and as ion channels. Because both the transmitter-binding function and the ion channel function are part of the same molecule, ionotropic receptors function very rapidly, typically opening in less than a millisecond after the transmitter binds. Although ionotropic receptors fall into different structural and genetic families than the superfamily of voltage-gated ion channels, they have in common the feature that they are composed of multiple membrane spanning subunits, with the pore formed at the interface between the subunits.

Metabotropic receptors do not themselves function as ion channels. Instead, the binding of the transmitter causes a structural change in the receptor which in turn activates a membrane-associated G-protein. The G protein then activates effector proteins, such as ion channels and membrane-associated enzymes. The mRs are all composed of polypeptide chains that snake through the membrane 7 times (starting with an extracellular N-terminus). They are sometimes called 7-spanning receptors or serpentine receptors. Because the activation of G-proteins is relatively slow (and the subsequent effects of G-proteins are also slow), synaptic transmission mediated via mRs is quite slow (100 msec or longer).

Individual synapses are quite small, and their actions quite weak. Therefore, in order to produce a suprathreshold depolarization, it is usually necessary that many excitatory synapses cooperate, especially if the postsynaptic cell is large, with a large capacitance and low input resistance. This cooperation can either be achieved by having many presynaptic axons each making only a few synapses, or by having few (perhaps only 1) presynaptic axons making many synapses. In the latter case, the collection of synapses made by a single axon essentially functions as a single powerful connection, which ensures that for every presynaptic spike a postsynaptic spike is reliably generated. Such synapses are often called multisynapses or relay synapses. In the former case, the probability of generating a postsynaptic spike depends on the number of active input connections and their strengths. We could call these "integrating" synapses because the postsynaptic cell combines or "integrates" the activities of the presynaptic cells. Integrating synapses perform the most interesting computations of brain cells, but we will first study an example of a relay synapses, the neuromuscular junction. Some neurons receive both types of synapse. For example, the output cells of the cerebellar cortex, the Purkinje cells,



Drawing of 2 Purkinje cells by the famour neuroanatomist Ramon y Cajal. His autobiography makes fascinating reading.

receive 2 types of excitatory input. They receive input from just 1 "climbing fiber" (the axon of neurons located in the inferior olivary nucleus of the medulla) and from 200,000 "parallel fibers" (the axons of the granule cells of the cerebellar cortex, which lie in a layer just below the layer of Purkinje cells). Each action potential in the climbing fiber causes a burst of action potentials in the Purkinje cell, while it takes several hundred parallel fibers firing together to cause a single spike in the Purkinje cell. We will see later that the Purkinje cell firing caused by PF input "sculpts" the details of complex precise movements, and that CF inputs "train" the PF inputs to produce more accurate movements.