Tutorial 12: Ionotropic Receptors in Postsynaptic Membranes

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Part 1: Image-Mapped Tutorial (Printable Version)
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Neurotransmitter receptor sites and their related, voltage-dependent ion channels compose a functional unit in the postsynaptic membrane. These units are called ionotropic receptors. In general, there are four major types of voltage-dependent channels. These control the passage of sodium, potassium, chloride and calcium ions across the membrane. The ion channel affected by a neurotransmitter determines whether or not a generated postsynaptic potential will be excitatory or inhibitory.

There are two different mechanisms, direct and indirect, by which these ion channels may be opened by the binding of a neurotransmitter. The simplest mechanism (*ion-channel linked receptors*) involves the direct opening of a channel coincident with the binding of a neurotransmitter to the receptor site. This effect is transient (milliseconds in duration). The indirect mechanisms involve a chain of chemical reactions that occur between the binding of a neurotransmitter to a receptor site and the opening of the channel. These are the mechanisms (*G-protein linked receptors* and *chemically-activated ion channels*) associated with the metabotropic neurotransmitters described in Tutorial 11 (hyperlink to figure11a, #10), and are sustained in nature (seconds to minutes in duration). The first indirect mechanism entails a metabotropic receptor site that is coupled to a G protein. When the neurotransmitter binds with the receptor site, the G protein nearby is activated. One of three units of the G protein, the alpha-subunit, breaks away and attaches to the ion channel. The binding of the alpha-subunit to the channel triggers its opening. The second type of indirect mechanism discovered involves the same complex (receptor site coupled to G protein) as just described. Except in this case, the activated alpha-subunit of the G protein activates an enzyme in the membrane that produces a *second messenger* molecule, which initiates a series of chemical events that open the channel.

Figure 12 illustrates the primary ionotropic mechanisms underlying the generation of excitatory and inhibitory postsynaptic potentials.

Advanced

More recent studies of neurotransmission have yielded a number of additional findings. Most neurotransmitters may combine with a number of different types of receptors. There are dozens of different G proteins in the typical postsynaptic membrane (Eckard & Beck-Sickinger, 2000; Soderling & Beavo, 2000). G proteins were named for guanylate triphosphate, the molecule that activates them; each has a specific protein target in the cell. Some of the second messengers created by activated G proteins have widespread effects (such as cyclic AMP). Others may activate certain target molecules (e.g., protein kinase A) that in turn activate other target molecules such as ion channels. In addition, some second messengers (e.g., cyclic AMP) may diffuse into the nucleus of the neuron to change the production of proteins by the genes within. These mechanisms may have long-range effects.

Two distinct systems of metabotropic receptors have been described, the cyclic nucleotide and the phosphoinositide systems. In the primary type of cyclic nucleotide system, the activating enzyme is

coupled to the receptor via a G protein. The G protein can either stimulate or inhibit the adenylate cyclase via its influence on the receptor. When the G protein activates this enzyme, cyclic AMP is produced (adenosine monophosphate). A series of reactions involving protein phosphorylations and dephosphorylations follow, resulting in the opening of specific ion channels; a synaptic potential is generated. A less common cyclic nucleotide system using the enzyme, guanylate cyclase, occurs predominantly in the cerebellum (Morris & Scarlata, 1997; Sharma & Duda, 1997; Sharma, Duda, Goraczniak & Sitaramayya, 1997).

The phosphoinositide system is considerably more complex (Catt, Hunyady & Balla, 1991; Conti & Jin, 1999; Pacheco & Jope, 1996). In one example of this type of system, the enzyme (phosphoinositidase C) is fixed deep within the lipid membrane layer adjacent to the neuroreceptors. Like the adenylate cyclase system, a G protein coupled to a neuroreceptor activates the enzyme. Triphosphoinositide is hydrolysed and the molecule, inositol triphosphate (IP3) is created. IP3 triggers the release of calcium ions from storage sites within the cell. The calcium, acting as a third messenger, initiates a series of protein phosphorylation reactions, which in turn open ion channels (e.g., potassium channels). The ionic flow generates the postsynaptic potential signaling an action potential. As mentioned before, the metabotropic response to neurotransmitter binding is much slower (10-30 X) than the more direct ionotropic response.

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Suggestions for further study

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