

# Chemical Messengers

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## Neurotransmitters: Amino Acids

In previous modules we examined the building blocks and structure of the nervous system. In this lesson we will discuss the chemical messengers that allow for communication within the system, the neurotransmitters. We will also cover the general characteristics of the action of drugs on the neurotransmitter system, a topic which we will cover in more detail in future lessons.

We'll begin this discussion with two of the simplest, yet most important neurotransmitters, GABA and glutamate. Both of these neurotransmitters are simple amino acids, yet they also constitute the most common inhibitory and excitatory neurotransmitters in the central nervous system. In fact, virtually all of the cell to cell communication that takes place in the CNS is due to these two simple amino acids, with the better known neurotransmitters serving in a moderating role.

**GABA** (gamma-aminobutyric acid) is the primary inhibitory neurotransmitter in the central nervous system. As a result it is, perhaps, the single most important. Inhibition in the brain is crucial in order to keep the neural signal organized and segmented. In fact, it is often said that the brain works primarily through inhibition, not excitation. GABA plays an important role in many physiological and behavioral processes. For example, the drug *Valium* (diazepam), which is often prescribed for anxiety disorders, increases GABA activity, as does **ethyl alcohol**. Two GABA receptors (A & B) have been identified. GABA<sub>A</sub> receptors are particularly complex, in that there are five different **binding sites** associated with the GABA<sub>A</sub> receptor. Each of these binding sites is particularly responsive to a given chemical substance. This means that the appropriate type of post synaptic potential will be initiated most effectively by this substance when it contacts the site, and the receptor is responsive to any of these substances given that they bind with the correct binding site. Three of these five binding sites are illustrated in Figure 1.

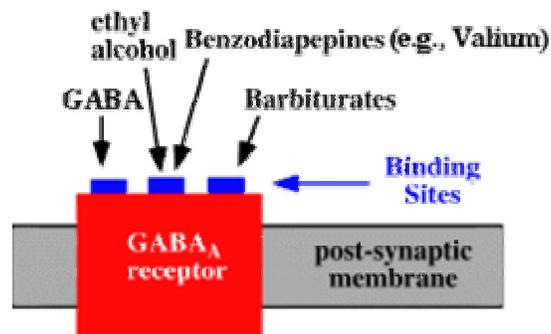


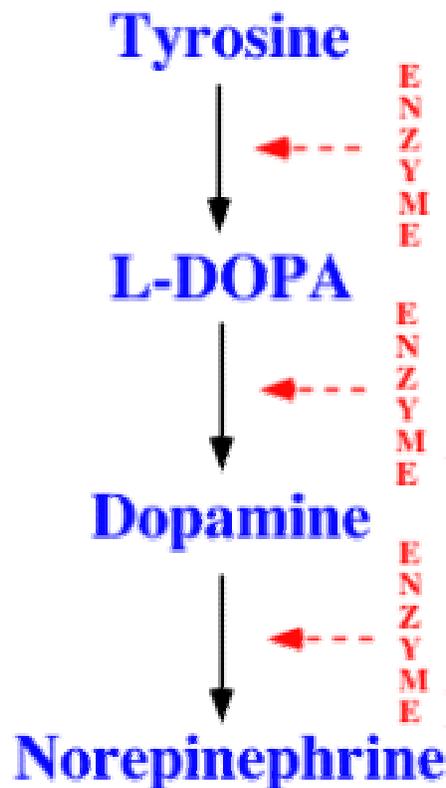
Figure 1. GABA<sub>A</sub> Binding Sites

**Glutamate**, is GABA's excitatory counterpart, in that Glutamate is the primary excitatory neurotransmitter in the central nervous system. Of course, glutamate also plays a very important role in many different neural processes, but it has been implicated as playing a particularly important role in learning and memory. For example, one type of Glutamate receptor **NMDA**, can result in alternations in neural synapses, so that new connections are formed, thus forming the neural basis for new memories.

### Neurotransmitters: Monoamines

As we move up a step in complexity of chemical structure, we come to the neurotransmitters that are more well known and studied. These are not, however, very chemically complex, or particularly large molecules. In fact, the monoamines, that we'll discuss in this section, and acetylcholine that we'll discuss in the next section are often referred to as **small molecule** neurotransmitters.

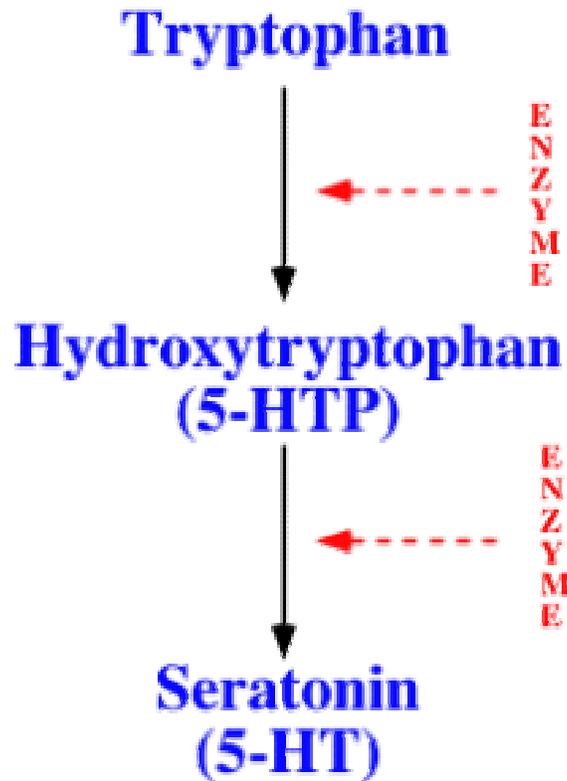
The **monoamines** include dopamine, norepinephrine, and serotonin. These can be further subdivided into **catecholamines** (dopamine and norepinephrine) and serotonin. It's easy to see why **dopamine** and **norepinephrine** are part of the same category since dopamine is a **precursor** for norepinephrine. A precursor is simply a substance that constitutes a preliminary step in the synthesis of another substance. In this case, dopamine interacts with an enzyme in the synthesis of norepinephrine. The major steps in the synthesis of dopamine and norepinephrine are presented in Figure 2.



**Figure 2.** Major Steps in Norepinephrine Synthesis

Norepinephrine was one of the first neurotransmitters identified since it is present in the peripheral nervous system. Norepinephrine is the neurotransmitter for synapses between sympathetic post-ganglionic nerves and their targets. In the central nervous system it appears to play an important role in attention and concentration among other things. As you will see in upcoming lessons, dopamine appears to play a role in many areas of psychology, such as schizophrenia, Parkinson's disease, and reinforcement.

Figure 3 is an illustration of the synthesis of **serotonin**. As with dopamine, serotonin plays an important role in many complex processes. In particular, we will read more about this neurotransmitter with respect to sleep and depression.



**Figure 3.** Major Steps in Serotonin Synthesis

### **Neurotransmitters: Acetylcholine**

The major steps in the synthesis of **acetylcholine** are illustrated in Figure 4. Acetylcholine was also one of the first neurotransmitters identified due to its presence in the peripheral nervous system. Acetylcholine is the neurotransmitter at all the motor-target synapses in the somatic branch of the peripheral nervous system. In addition, it is the neurotransmitter at the parasympathetic postganglionic-target synapses in the autonomic nervous system. (Recall that norepinephrine is the neurotransmitter at the corresponding sympathetic synapses.) In the central nervous system acetylcholine is best

known for its role in memory and learning. For example, Alzheimer's disease is associated with a break down in acetylcholine neurons.

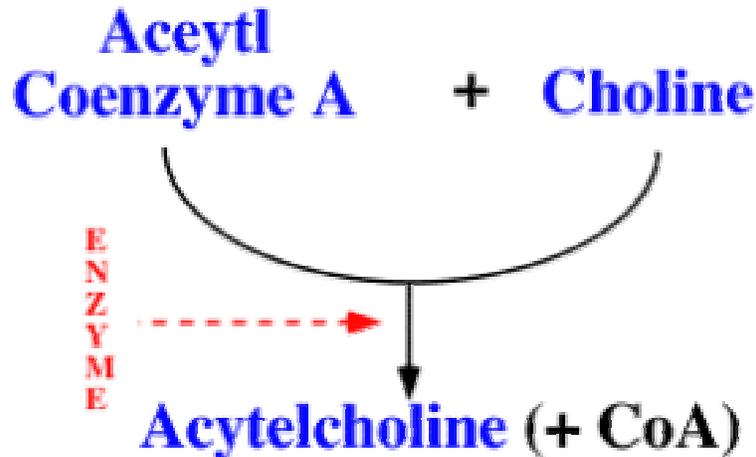


Figure 4. Major Steps in Acetylcholine Synthesis

### Neurotransmitters: Endorphins

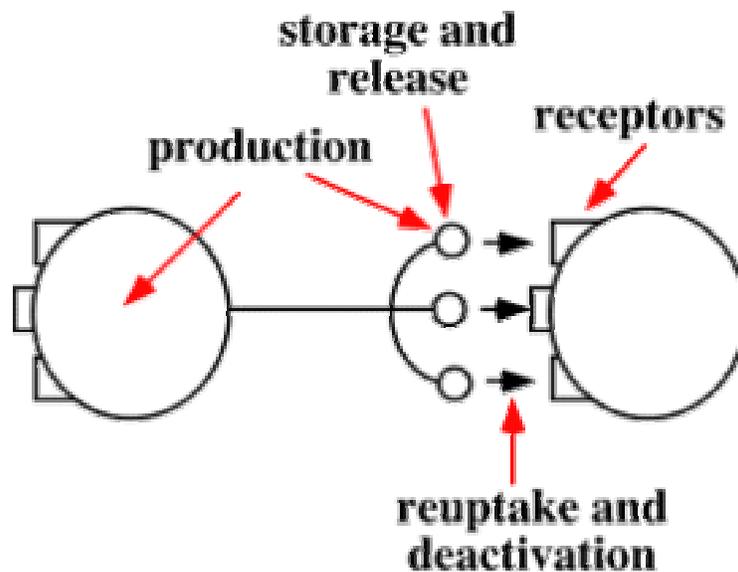
If you have heard of any of the neurotransmitters, chances are you've heard of **endorphins**. The term has come to be associated with feelings of pain relief, as in "the endorphins are kicking in." Athletes, in particular long distance runners, are said to experience a "runner's high" associated with endorphins. In fact, these labels are accurate, in the sense that endorphins play an important role in pain suppression, and as a result drugs that stimulate endorphins are reinforcing. The best known of these drugs are the opiates, morphine and heroin. In fact, the term "endorphin" refers to endogenous opiates, meaning opiates that are naturally occurring in the nervous system.

Unlike the other neurotransmitters discussed, endorphins are classified as **large molecule neurotransmitters**. Endorphins are formed from large peptides (combinations of many amino acids), which serve as precursors. For this reason they are one of a class of neurotransmitter referred to as **neuropeptides**. The other neurotransmitters discussed in this section primarily communicate only with adjacent neurons with which they form synapses. Large molecule neuropeptides, such as endorphins, on the other hand, not only release neurotransmitter from parts of the terminal button that are associated directly with receptors, but from other parts of the terminal button as well. Neurotransmitters released in this way act as **neuromodulators**, producing a diffuse effect on neurons in other locations in the brain.

### Pharmacology of the Synapse

The primary site of action for most **psychoactive drugs** (drugs that effect behavior) involves the neurotransmitters in one way or another. Such drugs, which we will talk about in more detail in other lessons, effect neurotransmitters in one of two fundamental ways, as agonist or antagonist. A drug is said to be an **agonist** for a given

neurotransmitter when its net effect is to enhance the activity of that neurotransmitter. Conversely, a drug is said to be an **antagonist** for a given neurotransmitter when the net effect is to decrease the activity of a neurotransmitter in some way. There are many different mechanisms by which the drugs can act as agonists or antagonists, and we will now discuss these as four general categories, which are illustrated in Figure 5. First, drugs can act to effect the production of neurotransmitters. This is why it's often necessary to know something about the synthesis of a given neurotransmitter in order to understand the effect of a drug on it. As you would expect, drugs that interfere with this synthesis act as antagonists, and drugs that enhance or stimulate this process act as agonists. An example of the latter is the drug **L-DOPA**, which is used in the treatment of Parkinson's disease. Parkinson's, a movement disorder, is due, in part, to a dysfunction involving dopamine activity. Since L-DOPA is a precursor for dopamine, the presence of additional amounts of the precursor results in large amounts of dopamine. Thus, L-DOPA acts as a dopamine agonist.



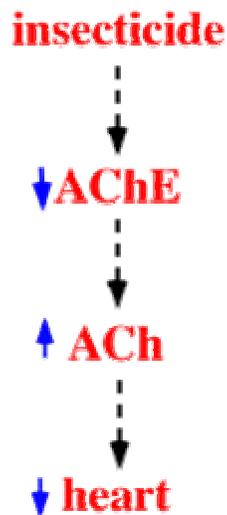
**Figure 5.** Mechanisms of Drug Action

Drugs can also stimulate or inhibit the storage and release of neurotransmitters, within the terminal button. Again, an antagonist would interfere in the process and an agonist would stimulate the process. An interesting and powerful example of this phenomenon is the poison **Botulinum toxin**, which inhibits the release of acetylcholine from the vesicles as they merge with cell membranes. This results in the paralysis of skeletal muscles, and suppression of the heart and lungs as well.

The most common mechanism by which drugs have their effect is via receptor sites. Drugs often "mimic" a neurotransmitter chemically, thus stimulating a given receptor site and producing the same effect as the neurotransmitter. These types of drugs act as agonists. Other drugs occupy receptor sites, but have no effect. Sort of like plugging a key hole with bubble gum. These drugs, on the other hand, act as antagonists. **Nicotine** acts as an acetylcholine agonist by mimicking acetylcholine on one type of acetylcholine

receptor. Such acetylcholine receptors are called, appropriately enough, **nicotinic** receptors.

A fourth general way in which drugs effect neurotransmitters is by inhibiting or stimulating the process of reuptake and/or deactivation. Unlike the other categories discussed, drugs that interfere with the process act as agonists and vice versa. A drug that inhibits deactivation, for example, allows for a neurotransmitter to remain in the synapse, thus increasing its effect. One relatively complex example of this process, depicted in Figure 6, is provided by some **insecticides** which work as acetylcholine agonists. These insecticides destroy the enzyme, AchE, which in turn increases the activity of acetylcholine. Since acetylcholine is the neurotransmitter at the target synapses in the parasympathetic nervous system, one of its roles is to slow the heart. If this activity is carried to extreme, the result is death. (Luckily, Humans and other mammals have an enzyme in their blood that destroys this insecticide before it can effect acetylcholine).



**Figure 6.** Insecticide Example of Impact on Reuptake and Deactivation