Neurotransmitters are the chemicals which account for the transmission of signals from one neuron to the next across synapses. They are also found at the axon endings of motor neurons, where they stimulate the muscle fibers to contract. And they and their close relatives are produced by some glands such as the pituitary and the adrenal glands. In this chapter, we will review some of the most significant neurotransmitters.

Acetylcholine was the first neurotransmitter to be discovered. It was isolated in 1921 by a German biologist named Otto Loewi, who would later win the Nobel Prize for his work. Acetylcholine has many functions: It is responsible for much of the stimulation of muscles, including the muscles of the gastro-intestinal system. It is also found in sensory neurons and in the autonomic nervous system, and has a part in scheduling REM (dream) sleep.

The well-known poison botulin works by blocking acetylcholin, causing paralysis. The botulin derivative botox is used by many people to temporarily eliminate wrinkles --a sad commentary on our times, I would say. On a more serious note, there is a link between acetylcholine and Alzheimer's disease: There is something on the order of a 90% loss of acetylcholine in the brains of people suffering from that debilitating disease.

In 1946, a Swedish biologist by the name of Ulf von Euler discovered norepinephrine (formerly called noradrenalin). He also won a Nobel Prize. Norepinephrine is strongly associated with bringing our nervous systems into "high alert." It is prevalent in the sympathetic nervous system, and it increases our heart rate and our blood pressure. Our adrenal glands release it into the blood stream, along with its close relative epinephrine (aka adrenalin). It is also important for forming memories.

Stress tends to deplete our store of adrenalin, while exercise tends to increase it. Amphetamines ("speed") work by causing the release of norepinephrine, as well as dopamine and serotonin (see below).

Another relative of norepinephrine and epinephrine is dopamine, discovered to be a neurotransmitter in the 1950s by another Swede, Arvid Carlsson. It is an inhibitory neurotransmitter, meaning that when it finds its way to its receptor sites, it blocks the tendency of that neuron to fire. Dopamine is strongly associated with reward mechanisms in the brain. Drugs like cocaine, opium, heroin, and alcohol increase the levels of dopamine, as does nicotine!

The severe mental illness schizophrenia has been shown to involve excessive amounts of dopamine in the frontal lobes, and drugs that block dopamine are used to help schizophrenics. On the other hand, too little dopamine in the motor areas of the brain are responsible for Parkinson's disease, which involves uncontrollable muscle tremors. It was the same Arvid Carlsson mentioned above who figured out that the precursor to dopamine (L-dopa) could elevate some of the symptoms. He was awarded the Nobel Prize in 2000. Recently, it has been noted that low dopamine may related not only to the unsociability of schizophrenics, but also to social anxiety. On the other hand, dopamine has been found to have relatively little to do with the pleasures of eating. That seems to involve chemicals such as endorphin (see below).

In 1950, Eugene Roberts and J. Awapara discovered GABA (gamma aminobutyric acid), which is also usually an inhibitory neurotransmitter. GABA acts like a brake to the excitatory neurotransmitters that lead to anxiety. People with too little GABA tend to suffer from anxiety disorders, and drugs like Valium work by enhancing the effects of GABA. Lots of other drugs influence GABA receptors, including alcohol and barbituates. If GABA is lacking in some parts of the brain, epilepsy results.
Glutamate is an excitatory relative of GABA. It is the most common neurotransmitter in the central nervous system -- as much as half of all neurons in the brain -- and is especially important in regards to memory. Curiously, glutamate is actually toxic to neurons, and an excess will kill them. Sometimes brain damage or a stroke will lead to an excess and end with many more brain cells dying than from the original trauma. ALS, more commonly known as Lou Gehrig's disease, results from excessive glutamate production. Many believe it may also be responsible for quite a variety of diseases of the nervous system, and are looking for ways to minimize its effects.

Glutamate was discovered by Kikunae Ikeda of Tokay Imperial Univ. in 1907, while looking for the flavor common to things like cheese, meat, and mushrooms. He was able to extract an acid from seaweed- glutamate. He went on to invent the well known seasoning MSG - monosodium glutamate. It took decades for Peter Usherwood to identify glutamate as a neurotransmitter in locusts in 1994.

Serotonin is an inhibitory neurotransmitter that has been found to be intimately involved in emotion and mood. Too little serotonin has been shown to lead to depression, problems with anger control, obsessive-compulsive disorder, and suicide. Too little also leads to an increased appetite for carbohydrates (starchy foods) and trouble sleeping, which are also associated with depression and other emotional disorders. It has also been tied to migraines, irritable bowel syndrome, and fibromyalgia.

Vittorio Erspamer first discovered what we now call serotonin in the 1930s. It was found in blood serum in 1948 by Irvine Page, who named it serotonin (from "serum-tonic"). Another researcher in Page’s lab - Maurice Rapport - proved that it was an amine. John Welsh found that it was a neurotransmitter in molluscs in 1954, and Betty Twarog (also at Page's lab) found it in vertebrates in 1952. All this gives you a sense of the cooperative nature of most of scientific discovery!

Prozac and other recent drugs help people with depression by preventing the neurons from "vacuuming" up excess seratonin, so that there is more floating around in the synapses. It is interesting that a little warm milk before bedtime also increases the levels of serotonin. As mom may have told you, it helps you to sleep. Serotonin is a derivative of tryptophan, which is found in milk. The "warm" part is just for comfort!

On the other hand, serotonin also plays a role in perception. Hallucinogens such as LSD, mescaline, psilocybin, and ecstasy work by attaching to serotonin receptor sites and thereby blocking transmissions in perceptual pathways.

In 1973, Solomon Snyder and Candace Pert of Johns Hopkins discovered endorphin. Endorphin is short for "endogenous morphine," i.e. built-in heroin! It is structurally very similar to the opioids (opium, morphine, heroin, etc.) and has similar functions: Inhibitory, it is involved in pain reduction and pleasure, and the opioid drugs work by attaching to endorphin's receptor sites. It is also the neurotransmitter that allows bears and other animals to hibernate. Consider: Heroin slows heart-rate, respiration, and metabolism in general -- exactly what you would need to hibernate. Of course, sometimes heroin slows it all down to nothing: Permanent hibernation.
NEUROTRANSMITTERS are the brain chemicals that communicate information throughout our brain and body. They relay signals between nerve cells, called “neurons.” The brain uses neurotransmitters to tell your heart to beat, your lungs to breathe, and your stomach to digest. They can also affect mood, sleep, concentration, weight, and can cause adverse symptoms when they are out of balance. Neurotransmitter levels can be depleted many ways. As a matter of fact, it is estimated that 86% of Americans have suboptimal neurotransmitter levels. Stress, poor diet, neurotoxins, genetic predisposition, drug (prescription and recreational), alcohol and caffeine usage can cause these levels to be out of optimal range.

There are two kinds of neurotransmitters – INHIBITORY and EXCITATORY. Excitatory neurotransmitters are not necessarily exciting – they are what stimulate the brain. Those that calm the brain and help create balance are called inhibitory. Inhibitory neurotransmitters balance mood and are easily depleted when the excitatory neurotransmitters are overactive.

**Inhibitory Neurotransmitters**

SEROTONIN is an inhibitory neurotransmitter – which means that it does not stimulate the brain. Adequate amounts of serotonin are necessary for a stable mood and to balance any excessive excitatory (stimulating) neurotransmitter firing in the brain. If you use stimulant medications or caffeine in your daily regimen – it can cause a depletion of serotonin over time. Serotonin also regulates many other processes such as carbohydrate cravings, sleep cycle, pain control and appropriate digestion. Low serotonin levels are also associated with decreased immune system function.

GABA is an inhibitory neurotransmitter that is often referred to as “nature’s VALIUM-like substance”. When GABA is out of range (high or low excretion values), it is likely that an excitatory neurotransmitter is firing too often in the brain. GABA will be sent out to attempt to balance this stimulating over-firing.

DOPAMINE is a special neurotransmitter because it is considered to be both excitatory and inhibitory. Dopamine helps with depression as well as focus, which you will read about in the excitatory section.

**Excitatory Neurotransmitters**

DOPAMINE is our main focus neurotransmitter. When dopamine is either elevated or low – we can have focus issues such as not remembering where we put our keys, forgetting what a paragraph said when we just finished reading it or simply daydreaming and not being able to stay on task. Dopamine is also responsible for our drive or desire to get things done – or motivation. Stimulants such as medications for ADD/ADHD and caffeine cause dopamine to be pushed into the synapse so that focus is improved. Unfortunately, stimulating dopamine consistently can cause a depletion of dopamine over time.

NOREPINEPHRINE is an excitatory neurotransmitter that is responsible for stimulatory processes in the body. Norepinephrine helps to make epinephrine as well. This neurotransmitter can cause ANXIETY at elevated excretion levels as well as some “MOOD
DAMPENING” effects. Low levels of norepinephrine are associated with LOW ENERGY, DECREASED FOCUS ability and sleep cycle problems.

EPINEPHRINE is an excitatory neurotransmitter that is reflective of stress. This neurotransmitter will often be elevated when ADHD like symptoms are present. Long term STRESS or INSOMNIA can cause epinephrine levels to be depleted (low). Epinephrine also regulates HEART RATE and BLOOD PRESSURE.
Characteristics of neurotransmitters

The number of known neurotransmitters has increased tremendously over the past several years. One of the earliest ones studied was acetylcholine, the most common neurotransmitter found in both invertebrates and vertebrates. It is the stimulating agent for skeletal muscle cells, but is the inhibiting agent for heart muscle cells, which demonstrates that the action of a neurotransmitter is influenced by the target receptor cells.

Norepinephrine, a catecholamine, is an example of a biogenic amine, which is derived from the amino acid tyrosine. It often works in an opposite way from acetylcholine in the autonomic nervous system and is also found in the cerebrum, cerebellum and spinal cord. Another catecholamine found in the brain is dopamine. It appears to be important in movement and regulating emotional responses.

A widely distributed neurotransmitter, serotonin, is found in blood platelets, the lining of the digestive tract, and the brain. It causes very powerful contractions of smooth muscle, and is associated with mood, attention, emotions, and sleep. LSD and mescaline, psychoactive drugs, mimic the structure and function of serotonin and other biogenic drugs to change the mental state of the user. Some new anti-depression drugs, for example, allow lengthened serotonin activity. One very common drug, Prozac (Fluoxetine), is a selective serotonin re-uptake inhibitor (SSRI). As the name implies, the drug inhibits the re-uptake of serotonin neurotransmitter from synaptic gaps, thus increasing neurotransmitter action. In the brain, then, the increased serotonin activity alleviates depressive symptoms.

One of the other amino acid derivatives, GABA (gamma-aminobutyric acid) is a major inhibitory transmitter in the central nervous system and it seems to play a role in Huntington's disease. In addition to the well known neurotransmitter, there are peptides, such as the opioids involved in killing pain and causing sleepiness, that act as neurotransmitters. Recently, certain gases, nitric oxide and carbon monoxide, have been discovered to be released from neurons. Nitric oxide has been found to diffuse to the nerves of the digestive system and govern the relaxation required for the normal movements of digestion.
Neurotransmitters and disease

Interest in the neurotransmitter is based on evidence that knowledge of how they function provides insight into the cause of some diseases, the effects of certain substances, and the behavior of organisms. Myasthenia gravis, which is a disease characterized by weakness of muscles and fatigue, is caused by a disturbance in the action of acetylcholine on skeletal muscles and is now treated by drugs that enhance the effect of acetylcholine. The discovery that dopamine-containing neurons in the brain of Parkinson's disease victims degenerate, which results in the shuffling gait and trembling characteristic of the disease, led to the use of levodopa, a compound that replaces dopamine.

Impairment of the dopamine system is also implicated in schizophrenia, a mental disease marked by disturbances in thinking and emotional reactions. Drugs, such as chlorpromazine and clozapine, that block dopamine receptors in the brain have been used to alleviate the symptoms and help patients return to a normal social setting. Depression, which afflicts about 3.5% of the population, is treated with antidepressants that affect norepinephrine and serotonin in the brain. The antidepressants help correct the abnormal excess or inhibition of signals that control mood, thoughts, pain, and other sensations. A new drug, fluoxetine, is a serotonin reuptake inhibitor which appears to establish the level of serotonin required to function at a normal level.

Alzheimer disease, which affects an estimated four million Americans, is characterized by memory loss and the eventual inability for self-care. The disease seems to be caused by a loss of cells in the basal forebrain which secrete acetylcholine. Some experimental drugs to alleviate the symptoms have been developed, but presently there is no known treatment for the disease.
The rise of drug addiction has directed attention to the role of neurotransmitters by attempting to understand how it happens and how it can be counteracted. Cocaine and crack are psychostimulants that affect neurons containing dopamine in the limbic and frontal cortex of the brain; when they are used they generate feelings of confidence and power. However, when large amounts are taken, people "crash" and suffer from physical and emotional exhaustion as well as depression. Opiates such as heroin and morphine appear to mimic naturally-occurring peptide substances in the brain with opiate activity called endorphins. Natural endorphins of the brain act to kill pain, cause sensations of pleasure, and cause sleepiness. Endorphins released with extensive aerobic exercise, for example, are responsible for the "rush" that long-distance runners experience.

It is believed that morphine and heroin combine with the endorphin receptors in the brain, resulting in reduced natural endorphin production. As a result, the drugs are needed to replace the naturally produced endorphins and addiction may occur. Attempts to counteract the effects involve using drugs that mimic them, such as nalorphine, naloxone, and naltrexone. One of the depressant drugs in widest use, alcohol, is believed to cause its effects by interacting with the GABA receptor. Initially anxiety is controlled, but greater amounts reduce muscle control and delay reaction time due to impaired thinking.
One of the most exciting areas of research is the attempt to find out how learning and memory take place. One of the earliest researchers who attempted to explain learning and memory as a function of cellular change was the Canadian psychologist, Donald O. Hebb. He maintained that repeated firing of axons results in metabolic changes in the presynaptic and post synaptic neurons. In other words, learning produces lasting chemical changes in nerve cells.

Aplysia, a marine snail with only 20,000 relatively large neurons, has been used in studies to determine the biological basis of learning. A conditioned reflex in Aplysia has been shown to cause an increase in the release of a neurotransmitter that sets up a chain of reactions, one of which also increases the secretion of serotonin from a modulating neuron.

In mammals, the hippocampus, part of the forebrain, stores long term memory for weeks before transferring it to the cerebral cortex. The transmitter used for long term potentiation is the amino acid, glutamate, which binds to receptors in the postsynaptic cell. This cell allows calcium to flow in and set up the activation of other molecules known as kinases.

A growing body of evidence implicates the role of dopamine as one of the most important chemicals that regulate cell activity involved in working memory. Studies done with aged monkeys show that a deficiency in both dopamine and norepinephrine in the prefrontal cortex can induce a deficit in working memory. Injections of the deficient neurotransmitters restored memory function. Progress in deciphering the operation of the nervous system has helped to increase knowledge of the diverse role of the neurotransmitter.