

**Review Article**

Common Neurotransmitters: Criteria for Neurotransmitters, Key Locations, Classifications and Functions

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To cite this article:Getinet Ayano. Common Neurotransmitters: Criteria for Neurotransmitters, Key Locations, Classifications and Functions. *American Journal of Psychiatry and Neuroscience*. Vol. 4, No. 6, 2016, pp. 91-95. doi: 10.11648/j.ajpn.20160406.12**Received:** June 4, 2016; **Accepted:** June 20, 2016; **Published:** March 10, 2017

Abstract: The criteria, key locations, classifications and functions of common neuro transmitters is reviewed and discussed. Neurotransmitters are the brain chemicals that communicate information throughout our brain and body. They relay signals between neurons. To be neurotransmitter the molecule must be present in the brain and distributed unevenly and enzymes that help to create the neurotransmitter must be present in the brain. Common inhibitory neurotransmitters such as serotonin, Gamma-amino butyric acid (GABA) and dopamine calm the brain and help create balance where as excitatory neurotransmitters such as norepinephrine, glutamate, epinephrine, and dopamine stimulate the brain. From inhibitory neurotransmitters dopamine is located in Amygdala, Cingulate cortex, Hippocampus, Nucleus accumbens. Olfactory bulb, Prefrontal cortex, substantia nigra and hypothalamus and it is mainly involved in movements, emotions, sexual arousal and cognitive functions where as Serotonin is located in Amygdala, Cingulate cortex, Hippocampus, thalamus, septum, neocortex, ventral tagemental area and hypothalamus and it is mainly involved in emotions, sleep, body temperature regulation and pain suppressions. From excitatory neurotransmitters norepinephrine is found in Amygdala, Hippocampus, brainstem, Spinal cord, Cerebellum, Cerebral cortex, Hypothalamus, Tectum, Thalamus, Ventral tegmental area, and Olfactory bulb and mainly involved in anxiety, mood, sympathetic arousal, cognitive control, working memory, hunger and circadian rhythm. Acetylcholine is found nucleus basalis of meynert, medial septal nucleus, diagonal band hippocampus, Cerebral cortex, limbic cortex, sensory cortex, thalamus and Ventral tegmental area and mainly involved in emotions, wakefulness and attention (arousal), short term memory, learning and motor functions.

Keywords: Neurotransmitters, Inhibitory Neurotransmitters, Excitatory Neurotransmitters, Monoamines

1. Neurons

Neurons are nerve cells. They are building blocks of the nervous system [1]. Neurons receives inputs, processes information, and generates outputs. The structure most associated with receiving is the dendrite, the structure most associated with processing is the cell body (also called soma), and the process most associated with the output is the axon, more specifically the terminal buttons. If we move to a slightly more detailed level we will find that neural signals most often are received by specialized areas on the dendrites called dendritic spines. As for the cell body, the "processing" actually occurs in the nucleus, within the cell body. Terminal buttons contain the chemical messengers [1, 2, 3].

Neurotransmitters are chemical messengers which are responsible for communication among neurons. Neurons are the cells of chemical communication in the brain. Human brains comprise tens of billions of neurons, each linked to thousands of other neurons. Thus, the brain has trillions of specialized connections known as synapses. Neurons have many sizes, lengths, and shapes which determine their functions. Localization within the brain also determines function. When neurons malfunction, behavioral symptoms may occur. When drugs alter neuronal function, behavioral symptoms may be relieved, worsened, or produced [2].

Infact, the brain, spinal cord, and nerves throughout the body are all made up of one kind of cell. These are nerve cells, also called neurons. Neurons communicate each other

(exchange message each other) by chemicals called neurotransmitters. A neuron message consists of chemical and electrical information's. Neurotransmitters cross the gaps between neurons. Each neuron may have thousands of branches that connect it to other neurons. The branches are called dendrites or axons. Dendrites carry messages toward the cell body. axons carry messages away from the cell body to another neuron. Axon tend as long as four feet in humans. In some animals, axons are even longer [1, 2].

2. Synapses

A synapse is the junction point between two neurons. However, a nerve impulse can also be transmitted from a sensory receptor cell to a neuron, or from a neuron to a set of muscles to make them contract, or from a neuron to an endocrine gland to make it secrete a hormone. In these last two cases, the connection points are called neuromuscular and neuro glandular junctions.

In a typical chemical synapse between two neurons, the neuron from which the nerve impulse arrives is called the presynaptic neuron [1, 2, 3]. The neuron to which the neurotransmitters (chemical messengers) bind is called the postsynaptic neuron.

A presynaptic neuron has several specialized structures that distinguish it from a postsynaptic neuron.

The terminal button of the presynaptic neuron's axon contains mitochondria as well as microtubules that transport the neurotransmitters from the cell body (where they are produced) to the tip of the axon.

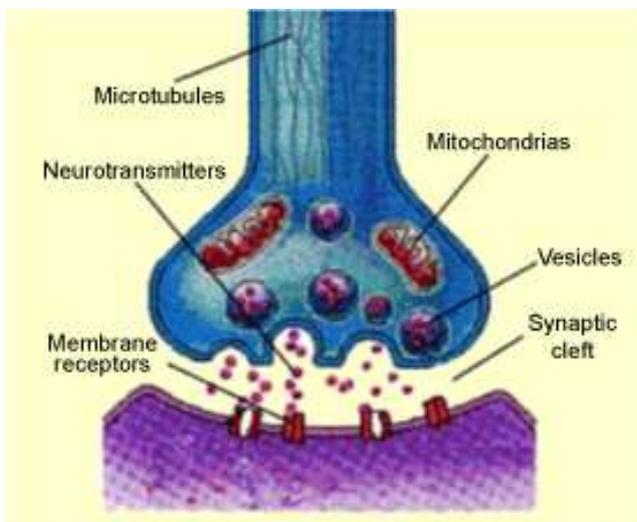


Figure 1. Structure of neurons.

This terminal button also contains spherical vesicles filled with neurotransmitters. These neurotransmitters are secreted into the synaptic gap by a process called exocytosis, in which the vesicles' membranes fuse with that of the presynaptic button. The synaptic gap that the neurotransmitters have to cross is very narrow—on the order of 0.02 micron. Across the gap, the neurotransmitters bind to membrane receptors: large proteins anchored in the cell membrane of the post-synaptic

neuron. At this location, under an electron microscope, you can observe an accumulation of opaque material which consists of the cluster of receptors and other signaling proteins that are essential for chemical neurotransmission [1, 2].

Any given neurotransmitter has several sub-types of receptors that are specific to it. It is the presence or absence of certain of these sub-types that causes a cascade of specific chemical reactions in the postsynaptic neuron. These reactions result in the excitation or inhibition of this neuron [4].

Axons and dendrites simply ran through the body continuously, like wires. There is space between each axon and dendrite. We call this space a synaptic gap, or synapse. The synapse is the space between the axon of one neuron and the dendrites of the next neuron in a nerve pathway. That gap is extremely small—about one-millionth of an inch. Chemical travel across the gaps. These chemicals are neurotransmitters [2, 4].

By far the most common types of synapses are those between an axon and a dendrite (axodendritic synapses) and those between an axon and the cell body of a neuron (axosomatic synapses). Other, less common kinds of synapses include axoaxonic synapses (involved in presynaptic inhibition phenomena) and dendrodendritic synapses [2, 4].

3. Neurotransmitters

Neurotransmitters, also known as chemical messengers, are endogenous chemicals that enable neurotransmission. They transmit signals across a chemical synapse, such as a neuromuscular junction, from one neuron (nerve cell) to another "target" neuron, muscle cell, or gland cell [4]. Neurotransmitters are released from synaptic vesicles in synapses into the synaptic cleft, where they are received by receptors on the target cells. Many neurotransmitters are synthesized from simple and plentiful precursors such as amino acids, which are readily available from the diet and only require a small number of biosynthetic steps for conversion. Neurotransmitters play a major role in shaping everyday life and functions. Their exact numbers are unknown, but more than 100 chemical messengers have been uniquely identified [5].

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 sub optimal neurotransmitter levels. Stress, poor diet, neurotoxins, genetic predisposition, drugs (prescription and recreational), alcohol and caffeine usage can cause these levels to be out of optimal range [5].

3.1. Neurotransmitters Meet Three Criteria

Neurotransmitters are molecules or groups of atoms, joined

by a chemical bond, that act as a unit. In order to be called a neurotransmitter, a molecule must meet three criteria [6, 7]:

First, the molecule must be present in the brain or must be synthesized in the neuron and distributed unevenly. That is, the molecule must be spread out among different types of neurons, and across regions of the brain that have different functions.

Second is a chemical criterion. The enzymes that help to create the neurotransmitter must be present in the brain. (An enzyme is a catalyst—a protein that speeds up chemical reactions within the body). Also, these enzymes must be present in areas where the neurotransmitter is found.

Third is the criterion of mimicry and excretion criteria. The same response must be obtained when the chemical is experimentally placed on the target and a mechanism must exist for removing the chemical from its site of activation after its work is done.

3.2. Types of Neurotransmitters

A neurotransmitter influences trans-membrane ion flow either to increase (excitatory) or to decrease (inhibitory) the probability that the cell with which it comes in contact will produce an action potential. Thus, despite the wide variety of synapses, they all convey messages of only these two types, and they are labeled as such. Type I synapses are excitatory in their actions, whereas type II synapses are inhibitory. Each type has a different appearance and is located on different parts of the neurons under its influence. Each neuron receives thousands of excitatory and inhibitory signals every second [1, 2, 8-11].

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.

Type I (excitatory) synapses are typically located on the shafts or the spines of dendrites, whereas type II (inhibitory) synapses are typically located on a cell body. In addition, Type I synapses have round synaptic vesicles, whereas the vesicles of type II synapses are flattened. The material on the presynaptic and post-synaptic membranes is denser in a Type I synapse than it is in a type II, and the type I synaptic cleft is wider. Finally, the active zone on a Type I synapse is larger than that on a Type II synapse.

3.2.1. 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 [2, 12].

Serotonin is a monoamine neurotransmitter. Most is produced by and found in the intestine (approximately 90%), and the remainder in central nervous system neurons. It functions to regulate appetite, sleep, memory and learning, temperature, mood, behavior, muscle contraction, and function of the cardiovascular system and endocrine system. It is speculated to have a role in depression, as some depressed patients are seen to have lower concentrations of metabolites of serotonin in their cerebrospinal fluid and brain tissue [12].

Serotonin is a chemical cousin of the "catecholamine's" 5HT, NE and DA are sometimes grouped under the heading MONOAMINES or BIOGENIC AMINES, and because of their similarities they are influenced by some of the same drugs. 5HT is best known as a transmitter in several brain areas [1, 2, 12]:

- 1) sleep regions
- 2) limbic system mood control regions
- 3) pain suppression system

The action of 5HT at a synapse is brought to an end primarily via reuptake. 5HT may also be broken down by the enzyme MAO. (think "5HT and SLeeP" for sleep, limbic mood control and pain suppression) [12-16].

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 [17].

GABA is used at the great majority of fast inhibitory synapses in virtually every part of the brain. Many sedative/tranquilizing drugs act by enhancing the effects of GABA [17]. Correspondingly, glycine is the inhibitory transmitter in the spinal cord.

Gamma-amino butyric acid (GABA:) GABA, another amino acid neurotransmitter widely distributed in the CNS, is the most important inhibitory transmitter [17].

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 [14].

Dopamine has a number of important functions in the brain; this includes regulation of motor behavior, pleasures related to motivation and also emotional arousal. It plays a critical role in the reward system; people with Parkinson's disease have been linked to low levels of dopamine and people with schizophrenia have been linked to high levels of dopamine [15].

DA is the precursor (chemical forerunner) that is turned into NE, so is closely related to NE and often affected by the same drugs. DA and NE are members of the transmitter family known as the CATECHOLAMINES. In some neurons the synthesis of transmitter stops at the DA step and DA serves as the neurotransmitter [14, 15, 18].

Key Locations and Functions:

DA is an important transmitter in several brain systems:

- 1) Extra pyramidal motor system (posture and movement

control)

- 2) Mesolimbic/mesocortical system (midbrain connections to limbic system and cortex) (emotion and cognitive functions)
- 3) Hypothalamus-pituitary system (menstrual and other hormone regulation) The action of DA at a synapse is brought to an end primarily via reuptake. (think "DAMMM" for motor, mood/ mesolimbic, menstrual/hormonal)

3.2.2. 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 day dreaming 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 [2, 14, 15, 18].

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 [19, 20].

Norepinephrine which focuses on the central nervous system, based on patients sleep patterns, focus and alertness. It is synthesized from tyrosine.

- 1) NE is the primary transmitter carrying messages from the sympathetic half of the autonomic nervous system to body organs and glands.
- 2) NE is a transmitter in many brain areas (reticular activating system, hypothalamus appetite areas, limbic system) and is involved in nervous system arousal, hunger, and mood control.

The action of NE at a synapse is brought to an end primarily via reuptake. NE may also be broken down by enzymes like MAO.(think "NE and hams" for hunger, arousal, mood, sympathetic) [14, 15, 19, 20].

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 [2, 14, 15].

Epinephrine which is also synthesized from tyrosine takes part in controlling the adrenal glands. It plays a role in sleep, with one's ability to stay become alert, and the fight-or-flight response

Other common neurotransmitters

Acetylcholine was the first neurotransmitter discovered in the peripheral and central nervous systems. It activates

skeletal muscles in the somatic nervous system and may either excite or inhibit internal organs in the autonomic system. It is distinguished as the transmitter at the neuromuscular junction connecting motor nerves to muscles. The paralytic arrow-poison curare acts by blocking transmission at these synapses. Acetylcholine also operates in many regions of the brain, but using different types of receptors, including nicotinic and muscarinic receptors [2, 19, 20].

Neurons which use ACh to send their messages are referred to as cholinergic neurons.

- 1) ACh is the transmitter at all neuromuscular (nerve-to-skeletal muscle) junctions. It stimulates all muscle contractions and hence all behavior.
- 2) ACh is the transmitter of the parasympathetic half of the autonomic nervous system.
- 3) ACh is a transmitter in many brain areas (cortex, basal ganglia, hypothalamus to name a few) and is necessary for normal memory and cognition and motor control.

The action of ACh released at a synapse is ended via breakdown of ACh by the enzyme acetylcholinesterase.

Glutamate is used at the great majority of fast excitatory synapses in the brain and spinal cord. It is also used at most synapses that are "modifiable", i.e. capable of increasing or decreasing in strength. Modifiable synapses are thought to be the main memory-storage elements in the brain. Excessive glutamate release can over stimulate the brain and lead to excitotoxicity causing cell death resulting in seizures or strokes. Excitotoxicity has been implicated in certain chronic diseases including ischemic stroke, epilepsy, Amyotrophic lateral sclerosis, Alzheimer's disease, Huntington disease, and Parkinson's disease. Glutamate, an amino acid, is the single most widely distributed excitatory neurotransmitter in the CNS [2, 8].

Histamine works with the central nervous system (CNS), specifically the hypothalamus (tuberomammillary nucleus) and CNS mast cells [15].

Endorphins (& enkephalins): A family of larger molecule transmitters involved in pain suppression, reward and positive mood states [2].

Classification (other means of classification)

There are many different ways to classify neurotransmitters. Dividing them into amino acids, peptides, and monoamines is sufficient for some classification purposes.

Major neurotransmitters:

- Amino acids: glutamate, aspartate, D-serine, γ -aminobutyric acid (GABA), glycine
- Gasotransmitters: nitric oxide (NO), carbon monoxide (CO), hydrogen sulfide (H₂S)
- Monoamines: dopamine (DA), norepinephrine (noradrenaline; NE, NA), epinephrine (adrenaline), histamine, serotonin (SER, 5-HT)
- Trace amines: phenethylamine, N-methylphenethylamine, tyramine, 3-iodothyronamine, octopamine, tryptamine, etc.
- Peptides: somatostatin, substance P, cocaine and amphetamine regulated transcript, opioid peptides [9]
- Purines: adenosine triphosphate (ATP), adenosine

- Others: acetylcholine (ACh), anandamide, etc.

4. Conclusions

Neurotransmitters are chemicals by which nerve cells or neurons communicate each other.

Serotonin, Gamma-aminobutyric acid (GABA) and dopamine are Common inhibitory neurotransmitters whereas as norepinephrine, glutamate, epinephrine, and dopamine are excitatory neurotransmitters.

Dopamine is located in Amygdala, Cingulate cortex, Hippocampus, Nucleus accumbens. Olfactory bulb, Prefrontal cortex, substantia nigra and hypothalamus and it is involved in movements, emotions, sexual arousal and cognitive functions where as Serotonin is located in Amygdala, Cingulate cortex, Hippocampus, thalamus, septum, neocortex, ventral tegmental area and hypothalamus and it is involved in emotions, sleep, body temperature regulation and pain suppressions.

Norepinephrine is found in Amygdala, Hippocampus, brain stem, Spinal cord, Cerebellum, Cerebral cortex, Hypothalamus, Tectum, Thalamus, Ventral tegmental area, and Olfactory bulb and involved in anxiety, mood, sympathetic arousal, cognitive control, working memory, hunger and circadian rhythm.

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