**PHYSIOLOGICAL ACTION AND MECHANISM OF NEUROTRANSMITTER**

**1.1. Introduction**

Neurotransmitters are chemicals that allow neurons to communicate with each other throughout the body. They enable the brain to provide a variety of functions, through the process of chemical synaptic transmission. These endogenous chemicals are integral in shaping everyday life and functions.  It is a type of chemical messenger which transmits signals across a [chemical synapse](https://en.wikipedia.org/wiki/Chemical_synapse), such as a [neuromuscular junction](https://en.wikipedia.org/wiki/Neuromuscular_junction), from one [neuron](https://en.wikipedia.org/wiki/Neuron) (nerve cell) to another "target" neuron, [muscle cell](https://en.wikipedia.org/wiki/Myocyte), or [gland cell](https://en.wikipedia.org/wiki/Gland).[[1]](https://en.wikipedia.org/wiki/Neurotransmitter#cite_note-1) Neurotransmitters are released from [synaptic vesicles](https://en.wikipedia.org/wiki/Synaptic_vesicles) in synapses into the [synaptic cleft](https://en.wikipedia.org/wiki/Synaptic_cleft), where they are received by [neurotransmitter receptors](https://en.wikipedia.org/wiki/Neurotransmitter_receptor) on the target cells. Many neurotransmitters are synthesized from simple and plentiful precursors such as [amino acids](https://en.wikipedia.org/wiki/Amino_acid), which are readily available from the diet and only require a small number of [biosynthetic](https://en.wikipedia.org/wiki/Biosynthetic) steps for conversion. Neurotransmitters play a major role in shaping everyday life and functions. Their exact numbers are unknown, but more than 200 unique chemical messengers have been identified.



**Figure 1. Structure of neurotransmitter**

*http://www.compoundchem.com/2015/07/30/*neurotransmitters*/*

Neurotransmitters are involved in the processes of early human development, including neurotransmission, differentiation, the growth of neurons, and the development of neural circuitry. Certain neurotransmitters may appear at different points of development. For example, monoamines are present before the neurons are differentiated. Norepinephrine levels are high in the notochord, even in the very early stages of the embryo. Serotonin has a role in morphogenesis. Excitatory amino acids tend to appear later in ontogenesis. The levels of neurotransmitters and neuromodulators tend to increase as new synapses form. Others will appear in the perinatal period, like glutamate, and plateau afterward. Hypoxia and drug-exposure can disturb the formation of neuronal circuity, leading to long-term deleterious effects in the body.

**1.2. Discovery**

Until the early 20th century, scientists assumed that the majority of synaptic communication in the brain was electrical. However, through the careful [histological](https://en.wikipedia.org/wiki/Histology) examinations by [Ramón y Cajal](https://en.wikipedia.org/wiki/Ram%C3%B3n_y_Cajal) (1852–1934), a 20 to 40 nm gap between neurons, known today as the [synaptic cleft](https://en.wikipedia.org/wiki/Synaptic_cleft), was discovered. The presence of such a gap suggested communication via chemical messengers traversing the synaptic cleft, and in 1921 German pharmacologist [Otto Loewi](https://en.wikipedia.org/wiki/Otto_Loewi) (1873–1961) confirmed that neurons can communicate by releasing chemicals. Through a series of experiments involving the vagus nerves of frogs, Loewi was able to manually slow the heart rate of frogs by controlling the amount of saline solution present around the vagus nerve. Upon completion of this experiment, Loewi asserted that sympathetic regulation of cardiac function can be mediated through changes in chemical concentrations. Furthermore, Otto Loewi is credited with discovering [acetylcholine](https://en.wikipedia.org/wiki/Acetylcholine) (ACh)—the first known neurotransmitter. Some neurons do, however, communicate via [electrical synapses](https://en.wikipedia.org/wiki/Electrical_synapse) through the use of [gap junctions](https://en.wikipedia.org/wiki/Gap_junction), which allow specific ions to pass directly from one cell to another.

**1.3. Mechanism**

Neurotransmitters are stored in [synaptic vesicles](https://en.wikipedia.org/wiki/Synaptic_vesicles), clustered close to the [cell membrane](https://en.wikipedia.org/wiki/Cell_membrane) at the [axon terminal](https://en.wikipedia.org/wiki/Axon_terminal) of the presynaptic neuron. Neurotransmitters are released into and diffuse across the [synaptic cleft](https://en.wikipedia.org/wiki/Synaptic_cleft), where they bind to specific [receptors](https://en.wikipedia.org/wiki/Receptor_%28biochemistry%29) on the membrane of the postsynaptic neuron.

Most neurotransmitters are about the size of a single amino acid; however, some neurotransmitters may be the size of larger proteins or [peptides](https://en.wikipedia.org/wiki/Peptides). A released neurotransmitter is typically available in the synaptic cleft for a short time before it is metabolized by enzymes, pulled back into the presynaptic neuron through [reuptake](https://en.wikipedia.org/wiki/Reuptake), or bound to a [postsynaptic receptor](https://en.wikipedia.org/wiki/Postsynaptic_receptor). Nevertheless, short-term exposure of the receptor to a neurotransmitter is typically sufficient for causing a postsynaptic response by way of [synaptic transmission](https://en.wikipedia.org/wiki/Neurotransmission).

In response to a threshold [action potential](https://en.wikipedia.org/wiki/Action_potential) or [graded electrical potential](https://en.wikipedia.org/wiki/Membrane_potential#Graded_potentials), a neurotransmitter is released at the presynaptic terminal. Low level "baseline" release also occurs without electrical stimulation. The released neurotransmitter may then move across the synapse to be detected by and bind with receptors in the postsynaptic neuron. Binding of neurotransmitters may influence the postsynaptic neuron in either an [inhibitory](https://en.wikipedia.org/wiki/Inhibitory_synapse) or [excitatory](https://en.wikipedia.org/wiki/Excitatory_synapse) way. This neuron may be connected to many more neurons, and if the total of excitatory influences are greater than those of inhibitory influences, the neuron will also "fire". Ultimately it will create a new action potential at its [axon hillock](https://en.wikipedia.org/wiki/Axon_hillock) to release neurotransmitters and pass on the information to yet another neighbouring neuron.



**Figure 2.** Synaptic vesicles containing neurotransmitters

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In the post-synatpic cell membrane of the receiving neuron, there are many receptors for the neurotransmitters. These receptors are basically large protein molecules to which the neurotransmitters bind. Think of the neurotransmitters and the receptors as “locks and keys”. Certain keys fit into certain locks. It is the same with neurotransmitters and receptors. When a neurotransmitter binds with a receptor, it either excites or inhibits the post-synaptic neurons. In the case of excitation, the neurotransmitter causes the post-synaptic neuron to generate an action potential and in the case of inhibition, the neurotransmitter prevents the post-synaptic neuron from generating an action potential.

**1.4. Identification**

There are four main criteria for identifying neurotransmitters:

1. The chemical must be synthesized in the neuron or otherwise be present in it.
2. When the neuron is active, the chemical must be released and produce a response in some targets.
3. The same response must be obtained when the chemical is experimentally placed on the target.
4. A mechanism must exist for removing the chemical from its site of activation after its work is done.

However, given advances in pharmacology, genetics, and chemical [neuroanatomy](https://en.wikipedia.org/wiki/Neuroanatomy%22%20%5Co%20%22Neuroanatomy), the term "neurotransmitter" can be applied to chemicals that:

* Carry messages between neurons via influence on the postsynaptic membrane.
* Have little or no effect on membrane voltage, but have a common carrying function such as changing the structure of the synapse.
* Communicate by sending reverse-direction messages that affect the release or reuptake of transmitters.

The anatomical localization of neurotransmitters is typically determined using immunocytochemical techniques, which identify the location of either the transmitter substances themselves or of the enzymes that are involved in their synthesis. Immunocytochemical techniques have also revealed that many transmitters, particularly the [neuropeptides](https://en.wikipedia.org/wiki/Neuropeptide%22%20%5Co%20%22Neuropeptide), are co-localized, that is, one neuron may release more than one transmitter from its synaptic terminal. Various techniques and experiments such as staining, stimulating, and collecting can be used to identify neurotransmitters throughout the [central nervous system](https://en.wikipedia.org/wiki/Central_nervous_system)

**1.5. Types**

There are many different ways to classify neurotransmitters. Dividing them into [amino acids](https://en.wikipedia.org/wiki/Amino_acids), [peptides](https://en.wikipedia.org/wiki/Peptides), and [monoamines](https://en.wikipedia.org/wiki/Monoamine) is sufficient for some classification purposes.

Major neurotransmitters:

* [**Amino acids**](https://en.wikipedia.org/wiki/Amino_acid)**:** [glutamate](https://en.wikipedia.org/wiki/Glutamate), [aspartate](https://en.wikipedia.org/wiki/Aspartate%22%20%5Co%20%22Aspartate), [D-serine](https://en.wikipedia.org/wiki/D-serine), [γ-aminobutyric acid](https://en.wikipedia.org/wiki/%CE%93-aminobutyric_acid) (GABA), [glycine](https://en.wikipedia.org/wiki/Glycine%22%20%5Co%20%22Glycine)
* [**Gasotransmitters**](https://en.wikipedia.org/wiki/Gasotransmitter)**:** [nitric oxide](https://en.wikipedia.org/wiki/Nitric_oxide) (NO), [carbon monoxide](https://en.wikipedia.org/wiki/Carbon_monoxide) (CO), [hydrogen sulfide](https://en.wikipedia.org/wiki/Hydrogen_sulfide) (H2S)
* [**Monoamines**](https://en.wikipedia.org/wiki/Monoamine)**:** [dopamine](https://en.wikipedia.org/wiki/Dopamine) (DA), [norepinephrine](https://en.wikipedia.org/wiki/Norepinephrine) , [epinephrine](https://en.wikipedia.org/wiki/Epinephrine) (adrenaline), [histamine](https://en.wikipedia.org/wiki/Histamine), [serotonin](https://en.wikipedia.org/wiki/Serotonin) (SER, 5-HT)
* **Traceamines:** [phenethylamine](https://en.wikipedia.org/wiki/Phenethylamine), [*N*-methylphenethylamine](https://en.wikipedia.org/wiki/N-methylphenethylamine), [tyramine](https://en.wikipedia.org/wiki/Tyramine), [3-iodothyronamine](https://en.wikipedia.org/wiki/3-iodothyronamine), [octopamine](https://en.wikipedia.org/wiki/Octopamine), [tryptamine](https://en.wikipedia.org/wiki/Tryptamine), etc.
* [**Peptides**](https://en.wikipedia.org/wiki/Peptide)**:** [oxytocin](https://en.wikipedia.org/wiki/Oxytocin%22%20%5Co%20%22Oxytocin), [somatostatin](https://en.wikipedia.org/wiki/Somatostatin%22%20%5Co%20%22Somatostatin), [substance P](https://en.wikipedia.org/wiki/Substance_P), [cocaine and amphetamine regulated transcript](https://en.wikipedia.org/wiki/Cocaine_and_amphetamine_regulated_transcript), [opioid peptides](https://en.wikipedia.org/wiki/Opioid_peptide%22%20%5Co%20%22Opioid%20peptide)[[11]](https://en.wikipedia.org/wiki/Neurotransmitter#cite_note-pmid38738-12)
* [**Purines**](https://en.wikipedia.org/wiki/Purinergic_signalling)**:** [adenosine triphosphate](https://en.wikipedia.org/wiki/Adenosine_triphosphate) (ATP), [adenosine](https://en.wikipedia.org/wiki/Adenosine)
* [**Catecholamines**](https://en.wikipedia.org/wiki/Catecholamine): [dopamine](https://en.wikipedia.org/wiki/Dopamine), [norepinephrine](https://en.wikipedia.org/wiki/Norepinephrine) (noradrenaline), [epinephrine](https://en.wikipedia.org/wiki/Adrenaline)
* Others: [acetylcholine](https://en.wikipedia.org/wiki/Acetylcholine) (ACh), [anandamide](https://en.wikipedia.org/wiki/Anandamide%22%20%5Co%20%22Anandamide), etc.

In addition, over 50 neuroactive [peptides](https://en.wikipedia.org/wiki/Peptide) have been found, and new ones are discovered regularly. Many of these are "co-released" along with a small-molecule transmitter. Nevertheless, in some cases, a peptide is the primary transmitter at a synapse. [β-endorphin](https://en.wikipedia.org/wiki/%CE%92-endorphin) is a relatively well-known example of a peptide neurotransmitter because it engages in highly specific interactions with [opioid receptors](https://en.wikipedia.org/wiki/Opioid_receptors%22%20%5Co%20%22Opioid%20receptors) in the [central nervous system](https://en.wikipedia.org/wiki/Central_nervous_system).