Review Article

Neurotransmitters – A biochemical view

Mohammed H F Shalayel[1*], Saadeldin A Idris[2], Mohammed Al-Noaemi[3] and Salah A M Ahmed[4]

Abstract:
The neurotransmission at most if not all synapses is chemical and is of great biochemical, physiological and pharmacological importance. Neurons communicate with each other at synapses by a process called synaptic transmission in which the release of small quantities of *chemical messengers,* called *neurotransmitters* that alter the electrical activity of neurons after they interact with receptors on post-synaptic cell surfaces. This review gives a biochemical view on the nature of neurotransmitters and presents the biochemical chart and the medical relevance of the most important neurotransmitters.

Keywords: Neurotransmitter, Synaptic vesicles, Acetylcholine (ACh), g -Aminobutyrate (GABA), Myasthenia Gravis (MG), Parkinson's disease, Opioid peptides.

The central nervous system (CNS) operates by a fine-tuned balance between excitatory and inhibitory signaling[1]. Complex brain functions, such as learning and memory, are believed to involve changes in the efficiency of communication between nerve cells. Therefore, the elucidation of the molecular mechanisms that regulate synaptic transmission, the process of intercellular communication, is an essential step towards understanding nervous system function[2]. The release of neurotransmitter via regulated exocytosis is the primary mode of communication in the nervous system[3].

Neurotransmitters are chemical substances which relay amplify and modulate signals between a neuron and another cell; i.e. involved in the transmission of an impulse from one cell to another[3]. The major categories of substances that act as neurotransmitters are[1] **amino acids** or amino acid derivatives (primarily glutamic acid, GABA, aspartic acid and glycine)[2], **peptides** (vasopressin, adrenocortitrophic hormone (ACTH), melanocyte stimulating hormone (MSH), somatostatin, neurotensin, β-endorphin, substance P, enkephalins etc.) and[3] **monoamines (biogenic amines)** (norepinephrine, dopamine, histamine, and serotonin) in addition to **acetylcholine**[4,5].

Neurotransmitters derived from amino acids include g -aminobutyrate, 5-hydroxytryptamine (serotonin), dopamine, norepinephrine, and epinephrine. Many drugs used to treat neurologic and psychiatric conditions affect the metabolism of these neurotransmitters[6].

Arginine is also the precursor of the intercellular signaling molecule nitric oxide (NO) that serves as a neurotransmitter (modulation of transmission), smooth muscle relaxant, and vasodilator. Synthesis of NO, catalyzed by NO synthase, involves the NADPH-dependent reaction of L-arginine with O_2 to yield L-citrulline and NO[6].

g -Aminobutyrate

g -Aminobutyrate (GABA) functions in brain tissue as an inhibitory neurotransmitter by altering trans-membrane potential differences. It is formed by decarboxylation of L-glutamate, a reaction catalyzed by L-glutamate decarboxylase[5] which needs pyridoxal phosphate (active vitamine B6) as a coenzyme. This process converts the principal excitatory neurotransmitter (glutamate) into

1. Department of Biochemistry, National College for Medical and Technical Studies, Khartoum, Sudan[1]
2. Faculty of Medicine, Western Kordufan University, Elnihood, Sudan[2]
3. Department of Physiology, National College for Medical and Technical Studies, Khartoum, Sudan[3]
4. Department of Biochemistry, Faculty of Medicine, University of Khartoum[4]
* correspondence: drmhfs@hotmail.com

the principal inhibitory one (GABA)[7,8]. Transamination of g -aminobutyrate forms succinate semialdehyde, which may then undergo reduction to g -hydroxybutyrate, a reaction catalyzed by L-lactate dehydrogenase, or oxidation to succinate and thence via the citric acid cycle to CO_2 and H_2O. A rare genetic disorder of GABA metabolism involves a defective GABA aminotransferase, an enzyme that participates in the catabolism of GABA subsequent to its postsynaptic release in brain tissue[6]. The brain's principal inhibitory neurotransmitterGABA, along with serotonin and norepinephrine, is one of several neurotransmitters that appear to be involved in the pathogenesis of anxiety and mood disorders[9].

There are two principal subtypes of postsynaptic GABA receptor complexes, the GABA-A and GABA-B receptor complexes. Activation of the GABA-B receptor by GABA causes neuronal membrane hyperpolarization and a resultant inhibition of neurotransmitter release. In addition to binding sites for GABA, the GABA-A receptor has binding sites for benzodiazepines, barbiturates, and neurosteroids. GABA-A receptors are coupled to chloride ion channels; activation of the receptor induces increased inward chloride ion flux, resulting in membrane hyperpolarization and neuronal inhibition[9].

Other inhibitory neurotransmitters include glycine, β-alanine, and taurine as well as histamine while, the dicarboxylic amino acids glutamate and aspartate are excitatory ones[10].

The membranes of **nerve cells** contain well-studied ion channels that are responsible for the action potentials generated across the membrane. The activity of some of these channels is controlled by neurotransmitters; hence, channel activity can be regulated. One ion can regulate the activity of the channel of another ion. For example, a decrease of Ca+2concentration in the extracellular fluid increases membrane permeability and increases the diffusion of Na^+. This depolarizes the membrane and triggers nerve discharge, which may explain the numbness, tingling, and muscle cramps symptoms of a low level of plasma Ca^{2+}.[6]

Neurons (nerve cells) and certain muscle cells are specialized to generate and conduct a particular type of electric impulse, the **action potential.** This alteration of the electric potential across the cell membrane is caused by the opening and closing of certain voltage-gated ion channels[11].

Arrival of an action potential at an axon terminal (figure 1) leads to opening of voltage-sensitive Ca+2channels and an influx of Ca^{2+}, causing a localized rise in the cytosolic Ca+2concentration in the axon terminus. The rise in Ca+2in turn triggers fusion of small vesicles containing neurotransmitters with the plasma membrane, releasing neurotransmitters from this *presynaptic cell* into the synaptic cleft, the narrow space separating it from *postsynaptic cells*. It takes about 0.5 millisecond (ms) for neurotransmitters to diffuse across the synaptic cleft and bind to a receptor on the postsynaptic cell. Binding of neurotransmitter triggers opening or closing of specific ion channels in the plasma membrane of postsynaptic cells, leading to changes in the membrane potential at this point.

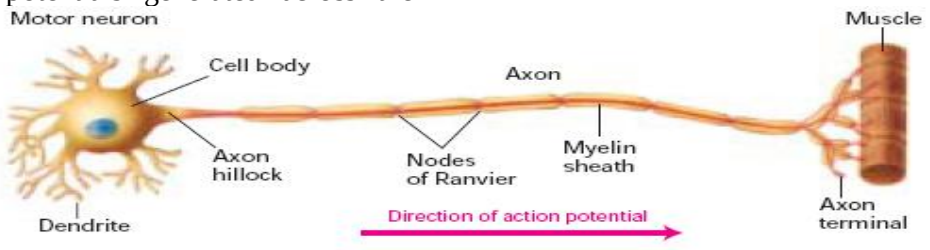


Figure 1: Arrival of an action potential at an axon terminal

A single axon in the central nervous system can synapse with many neurons and induce responses in all of them simultaneously. Thus neurons use changes in the membrane potential, the action potentials, to conduct signals along their length, and small molecules, the neurotransmitters, to send signals from cell to cell[11].

Synapses are the junctions where neurons release a chemical neurotransmitter that acts on a postsynaptic target cell, which can be another neuron or a muscle or gland cell. Neurotransmitter receptors fall into two broad classes: **ligand-gated ion channels**, which open immediately upon neurotransmitter binding, and **G protein–coupled receptors**. Neurotransmitter binding to a G protein–coupled receptor induces the opening or closing of a *separate* ion channel protein over a period of seconds to minutes[6,11].

Numerous small molecules function as neurotransmitters at various synapses. With the exception of **acetylcholine** (figure 2)**,** the neurotransmitters shown in Figure 3 are amino acids or derivatives of amino acids. Nucleotides such as ATP and the corresponding nucleosides, which lack phosphate groups, also function as neurotransmitters. Each neuron generally produces just one type of neurotransmitter[11].

All the "classic" neurotransmitters are synthesized in the cytosol and imported into membrane-bound synaptic vesicles within axon terminals, where they are stored. Similar to the accumulation of metabolites in plant vacuoles, this proton concentration gradient (vesicle lumen cytosol) powers neurotransmitter import by ligand-specific H^+-linked antiporters in the vesicle membrane. For example, acetylcholine is synthesized from acetyl coenzyme A (acetyl CoA), an intermediate in the degradation of glucose and fatty acids, and choline in a reaction catalyzed by choline acetyltransferase[11]:

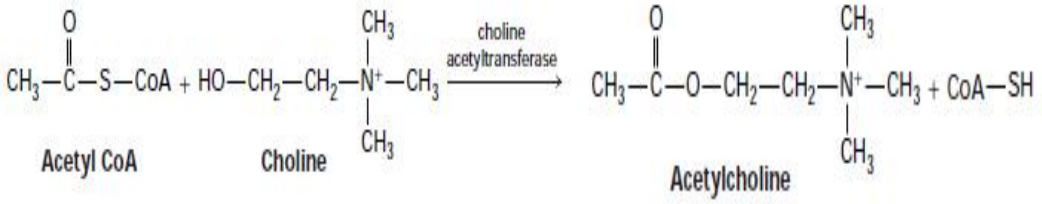


Figure 2: Synthesis of acetylcholine from acetyl-CoA and choline

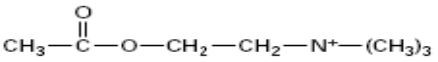
Synaptic vesicles take up and concentrate acetylcholine from the cytosol against a steep concentration gradient, using an H^+/acetylcholine antiporter in the vesicle membrane. Curiously, the gene encoding this antiporter is contained entirely within the first intron of the gene encoding choline acetyltransferase, a mechanism conserved throughout evolution for ensuring coordinate expression of these two proteins. Different H^+/neurotransmitter antiport proteins are used to import other neurotransmitters into synaptic vesicles[11].

Neurotransmitters are released by **exocytosis,** a process in which neurotransmitter-filled synaptic vesicles fuse with the axonal membrane, releasing their contents into the synaptic cleft.

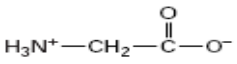
The exocytosis of neurotransmitters from synaptic vesicles involves vesicle-targeting and fusion events similar to those that occur during the intracellular transport of secreted and plasma-membrane proteins. Two features critical to synapse function differ from other secretory pathways: (a) secretion is tightly coupled to arrival of an action potential at the axon terminus, and (b) synaptic vesicles are recycled locally to the axon terminus after fusion with the plasma membrane[11].

Acetylcholine (ACh) was the neurotransmitter first discovered, at the beginning of the last century. It binds to two types of receptor; the **nicotinic ACh receptor** responds to the alkaloid *nicotine* contained in tobacco, and the **muscarinic ACh receptors** (of which

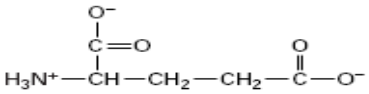
there are at least five subtypes) are metabotropic.



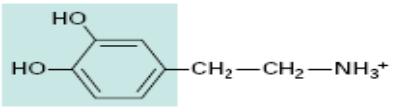
Acetylcholine



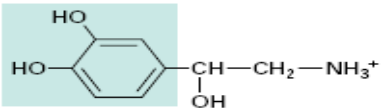
Glycine



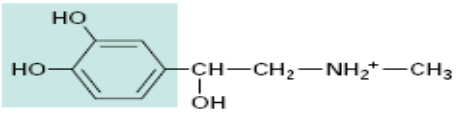
Glutamate



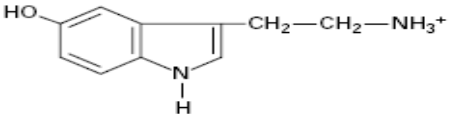
Dopamine
(derived from tyrosine)



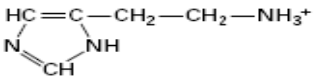
Norepinephrine
(derived from tyrosine)



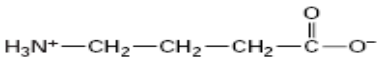
Epinephrine
(derived from tyrosine)



Serotonin, or **5-hydroxytryptamine**
(derived from tryptophan)



Histamine
(derived from histidine)



γ-Aminobutyric acid, or **GABA**
(derived from glutamate)

Their name is derived from the alkaloid *muscarine,* which is found in the flyagaric mushroom (*Amanita muscaria*), for example. Like ACh, muscarine is bound at the receptor, but in contrast to ACh, it is not broken down and therefore causes permanent stimulation of muscle[12].

The acetylcholine receptor is a ligand-gated sodium channel that initiates the flow of sodium into the cell (and potassium out) when the receptor binds the neurotransmitter, acetylcholine. Voltage-gated channels open and close in response to changes in the membrane potentials. The acetylcholine receptor is also voltage-gated. When the membrane potential becomes positive, it opens the channel further, increasing the rate of membrane depolarization[13]. Following their release from a presynaptic cell, neurotransmitters must be removed or destroyed to prevent continued stimulation of the postsynaptic cell. Signaling can be terminated by diffusion of a transmitter away from the synaptic cleft, but this is a slow process. Instead, one of two more rapid mechanisms terminates the action of neurotransmitters at most synapses. Signaling by acetylcholine is terminated when it is hydrolyzed to acetate and choline by *acetylcholinesterase,* an enzyme localized to the synaptic cleft. Choline released in this reaction is transported back into the presynaptic axon terminal by a Na^+/choline symporter and used in synthesis of more acetylcholine. The operation of this transporter is similar to that of the Na^+-linked symporters used to transport glucose into cells against a concentration gradient. With the exception of acetylcholine, all the neurotransmitters are removed from the synaptic cleft by transport into the axon terminals that released them. Thus these transmitters are recycled intact. Transporters for GABA, norepinephrine, dopamine, and serotonin were the first to be cloned and studied. These four transport proteins are all Na^+-linked symporters. They are 60–70 percent identical in their amino acid sequences, and each is thought to contain 12 transmembrane α helices. As with other Na^+ symporters, the movement of Na^+ into the cell down its electrochemical gradient provides the energy for uptake of the neurotransmitter. To maintain electroneutrality, Cl^+ is often

transported via an ion channel along with the Na^+ and neurotransmitter.

The neurotransmitters released from presynaptic neurons may bind to an *excitatory receptor* on the postsynaptic neuron, thereby opening a channel that admits Na^+ ions or both $Na^+$and K^+ ions[11].

The acetylcholine receptor is one of many excitatory receptors, and opening of such ion channels leads to depolarization of the postsynaptic plasma membrane, promoting generation of an action potential[11,13]. In contrast, binding of a neurotransmitter to an *inhibitory receptor* on the postsynaptic cell causes opening of K^+ or Cl^+ channels, leading to an efflux of additional K^+ ions from the cytosol or an influx of Cl^+ ions. In either case, the ion flow tends to hyperpolarize the plasma membrane, which inhibits generation of an action potential in the postsynaptic cell[11].

The neuromuscular junction consists of a single nerve terminal separated from the post-synaptic region by the **synaptic cleft** (figure 4). The motor end plate is the specialized portion of the muscle membrane involved in the junction. **Junctional folds** are prominent; they contain a high density of AChRs in close proximity to the nerve terminal.

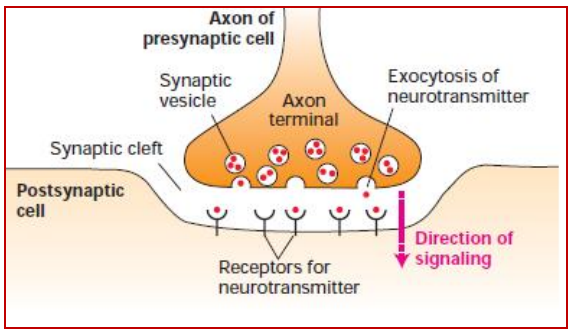


Figure 4: A chemical synapse.

The overall process at the junction can be considered to take place in six steps:

1. Synthesis of acetylcholine occurs in the cytosol of the nerve terminal (**terminal knob**). In a reaction catalyzed by choline acetyl transferase.
2. Acetyl choline is then incorporated into small membrane-bound particles called **synaptic vesicles** and stored there.
3. Release of acetylcholine from these vesicles into synaptic cleft is the next step. This occurs by exocytosis, which involves fusion of the vesicles with the pre-synaptic membranes. In the resting state, single quanta (~ 10,000 transmitter molecules, probably corresponding to the contents of one synaptic vesicle) are released spontaneously, resulting in small end plate potentials. When a nerve ending is depolarized by transmission of a nerve impulse, this process opens voltage-sensitive Ca^{++} channels, permitting an influx of $Ca^{+2}$from synaptic space (cleft) into the nerve terminal. This Ca^{+2}plays an essential role in the exocytosis that releases acetylcholine (contents of approximately 200 vesicles) into the synaptic space.
4. The released acetylcholine diffuses across the synaptic cleft to its receptors in the junctional folds. When 2 molecules of acetylcholine bind to a receptor, it undergoes a conformational change, opening a channel in the receptor that permits a flux of cations (Na^+) across the membrane. The consequent entry of Na^+ results in depolarization of the muscle membrane, forming end plate potential. This in turns depolarizes the adjacent muscle membrane, and action potentials are generated and transmitted along the fiber, resulting in contraction. Thus, AChR (acetylcholine receptor) is a

transmitter-gated ion channel. (**N.B** some neurotransmitters can inhibit the post-synaptic membrane by altering its permeability to Cl^- or K^+).

5. When the channel closes, the acetylcholine dissociates and is hydrolyzed by acetylcholine esterase to acetate and choline. This important enzyme is present in high concentrations in basal lamina of the synaptic space.

6. Choline is recycled into the nerve terminal by an active transport mechanism, where it can be used again for synthesis of acetylcholine[5,14].

Catecholamines:

Catecholamines (epinephrine, norepinephrine, and dopamine) are amine hormones derived from the amino acid tyrosine. They act as neurotransmitters in the central and peripheral nervous systems. The catecholamine hormones travel in the blood to their target cell and bind to the plasma membrane at specific receptor sites. Binding of catecholamine activates the cyclic AMP second messenger system and alters enzyme activity or membrane permeability.

The fight-or-flight response begins with activation of the sympathetic nervous system (SNS), a branch of the autonomic nervous system (ANS). Immediately following stressor exposure, the SNS responds with the release of the catecholamines epinephrine and norepinephrine from sympathetic neurons and the adrenal medulla, located in the center of the adrenal glands.

The responses to catecholamines are similar whether they are released from nerves or from the adrenal medulla. However, catecholamines released from the adrenal gland are rapidly metabolized and thus show more limited effects. Norepinephrine works both as a neurotransmitter in the CNS and as a hormone when it is released by the adrenal gland with epinephrine. Circulating and neurally released norepinephrine binds to receptors called alpha-receptors, identified as alpha1 and alpha 2 receptors. Binding to alpha1 receptors present on most vascular smooth muscle cells causes the muscles to contract, leading to a decrease in blood flow to organs supplied by those vascular beds. By this means, sympathetic activation causes a decrease in blood flow to the organs of the gastrointestinal (GI) tract, the skin, and the kidneys. Decreasing blood flow to these organs ensures maximum blood flow to the brain, heart, and skeletal muscles in times of stress. Norepinephrine also binds to receptors on the smooth muscle of the GI tract, causing relaxation of the muscle and thereby slowing digestion and GI motility. Circulating and neurally released epinephrine acts by binding not only to alpha-receptors, but also to beta-receptors, identified as β_1 and β_2. By binding to β_1 receptors on the heart, epinephrine causes an increase in heart rate and an increase in cardiac contractility, both of which serve to increase the cardiac output during stress. Epinephrine binding to β_2 receptors in the liver and skeletal muscle causes an increase in glucose release, resulting in increased glucose available for all cells to use if fight or flight is necessary. Epinephrine binding to β_2 receptors present on bronchiolar smooth muscle increases airflow to the lungs by relaxing the muscle, thereby opening up the air passages and facilitating oxygenation of blood for tissues that may be called on during a stressful situation[15].

The secretion of prolactin from the anterior pituitary is under the control of two opposing hypothalamic hormones: prolactin-inhibitory hormone (PIH) and prolactin-stimulatory hormone. PIH appears to be the neurotransmitter dopamine thus, a decrease in the release of dopamine stimulates prolactin release[15].

Serotonin:

Serotonin (5-hydroxytryptamine or 5-HT) is a monoamine neurotransmitter synthesized in

serotonergic neurons in the central nervous system and enterochromaffin cells in the gastrointestinal tract. Serotonin is believed to play an important part of the biochemistry of depression, migraine, bipolar disorder and anxiety. It is also believed to be influential on sexuality and appetite. Serotonin is found extensively in the human gastrointestinal tract, or gut, as well as in the blood stream. In the body, serotonin is synthesized from the amino acid tryptophan by various enzymes as shown in the reaction below. Serotonin taken orally does not pass into the serotonergic pathways of the central nervous system (CNS). This is due to the blood-brain barrier's preventing serotonin in the blood stream from affecting serotonin levels in the brain. Moreover, the neurotransmitter serotonin plays a key role in stimulating neurons that participate in the storage of long-term memory[16].

ATP:

Purines have long been known for their roles in extracellular signaling. One of the most interesting functions to come to light recently has been the involvement, particularly of adenosine 5'-triphosphate (ATP), as a neurotransmitter in the central and the sympathetic nervous system. ATP is stored in and released from synaptic nerve terminals, like other neurotransmitters, and is known to act postsynaptically via specific rapidly-conducting, ligand-gated ion channels, the P_{2X} receptors. Another interesting feature is the discovery that ATP is widely found to be a "co-transmitter" at the same synapses in combination with other neurotransmitters such as noradrenaline, acetylcholine, and GABA, altering our picture of the biophysics and biochemistry of neurotransmission at these synapses[17]. Co-transmission has been described as the co-localization and co-release of two or more neurotransmitters upon nerve stimulation from the same nerve terminals, to act on the post-synaptic cells to carry out the process of neurotransmission. The actions of co-transmitters on the post-synaptic cells have been reported to be either synergistic or antagonistic[18].

Medical relevance:

- To understand Myasthenia Gravis (MG), it is necessary to understand events occurring at neuromuscular junction. MG is characterized by recurrent episodes of muscle weakness after exercise; muscles supplied by cranial nerves are most affected. It is improved by administration of drugs that inhibit acetylcholine esterase (e.g. the short acting edrophonium or longer acting agents like pyridostigmine and neostigmine), a fact that is used in diagnosis and treatment. In MG, for unclear reasons, the body forms auto-antibodies against the acetylcholine receptors of the neuromuscular junction[14].

- Acondition that resembles myasthenia gravis is **Lambert–Eaton syndrome.** In this condition, muscle weakness is caused by antibodies against one of the Ca^{+2}channels in the nerve endings at the neuromuscular junction. This decreases the normal Ca^{+2}influx that causes acetylcholine release. However, muscle strength increases with prolonged contractions as more Ca+2is released[19].

- Acetylcholine esterase is responsible for the hydrolysis of acetylcholine. It is very important that neurotransmitter has a very short half-life following its release from the pre-synaptic neurons. If acetylcholine esterase is inhibited (by the use of a nerve gas, diisopropylfluorophosphate, DFP), the muscles of the body undergo violent contraction due to the continued presence of high concentration of acetylcholine and finally become paralyzed[14].

- There are other highly toxic substances whose action comes from their disruption of normal nerve muscle communication. Curare is a powerful muscle relaxant that leads to paralysis and death by asphyxiation. Curare, used by South American Indians, competitively inhibits binding of ACh to its membrane receptor12.

- The bacterial toxin responsible for botulism (clostridium botulinum) also causes paralysis but, it acts by blocking the release of acetylcholine from presynaptic neuron. Botulinum neurotoxins (BoNT, serotypes A-G) and tetanus neurotoxin (TeNT) are bacterial proteins that comprise a light chain (Mr ≈50) disulfide linked to a heavy chain (Mr ≈100). By inhibiting neurotransmitter release at distinct synapses, these toxins cause two severe neuroparalytic diseases, tetanus and botulism. The cellular and molecular modes of action of these toxins have almost been deciphered. After binding to specific membrane acceptors, BoNTs and TeNT are internalized via endocytosis into nerve terminals. Subsequently, their light chain (a zinc-dependent endopeptidase) is translocated into the cytosolic compartment where it cleaves one of three essential proteins involved in the exocytotic machinery: vesicle associated membrane protein (also termed synaptobrevin), syntaxin, and synaptosomal associated protein of 25 kDa[20]. There are local anesthetics such as procaine that have similar mode of action (blocking the release of acetylcholine from presynaptic neuron)14.
- Parkinson's disease is caused by degeneration of the cells of the substantia nigra (atrophic changes in the substantia nigra and depletion of neurons in the locus coeruleus), resulting in a deficiency of dopamine in such cells. Levo dopa (L-dopa) is an effective therapy as it can cross the blood brain barrier and is converted to dopamine in the brain[10].

- Biochemical changes in brains of patients with Alzheimer's disease and senile dementia include reduced activity of acetylcholineesterase and choline-acetyltransferase, indicating reduced activity in the acetylcholinergic system. There is also, however, reduced activity in the dopamine, noradrenaline and 5-hydroxytryptamine system[21].

- Autoimmunity to glutamate decarboxylase (GAD) appears to cause the **stiff-man syndrome,** a disease characterized by fluctuating but progressive muscle rigidity and painful muscle spasms, presumably due to GABA deficiency. It is interesting that GAD is also present in structures resembling synaptic vesicles in the insulin-secreting β cells of the pancreas, and GABA may be a paracrine mediator in the islets[19].

- The classical dopamine hypothesis of schizophrenia postulates a hyperactivity of dopaminergic transmission at the D2 receptor and there is a direct evidence of increased stimulation of D2 receptors by dopamine in schizophrenia, consistent with increased phasic activity of dopaminergic neurons[22].

Biochemical chart and medical relevance of the major neurotransmitters are summarized[10,19,23,24] in table 1,2 and 3.

Neurotransmitter	Effect	Precursors or sources	Enzyme catalysts	Metabolites	Medical andclinical relevance
Acetylcholine	Excitatory	Choline, Acetyl-CoA	Choline acetyltransferase Acetylcholinesterase	Acetate, Choline	Alzheimer's, Myasthenia, Parkinson's, Huntington's chorea, Botulinum, Pesticide toxicity
Amino acids					
GABA	Inhibitory	Glutamate	Glutamate decarboxylase	Succinate	Epilepsy, Anxiety, Spasticity, Aggression, Delirium, Headache, Stiff-man syndrome
Glycine	Inhibitory Excitatory ?	Glyoxylate, Serine Or CO_2 + NH_4 + N^5,N^{10}-methenyltetrahydrofolate	Transaminase Serine hydroxymethyl transferase Glycine synthase (glycine cleavage enzyme)	Serine, CO_2 + NH_4	Startle syndromes Pain transmission by (NMDA) receptors in the dorsal horn
Glutamate Aspartate	Excitatory	α-ketoglutarate Oxaloacetate	Glutamate dehydrogenase Transaminase	GABA	Alzheimer's, Epilepsy, Cerebral ischemia, Depression, Motor neuron disease

Table 1: Biochemical chart and medical relevance of some major neurotransmitters

Neurotransmitter	Effect	Precursors or sources	Enzyme catalysts	Metabolite	Medical andclinical relevance
Neuropeptides	Excitatory and inhibitory				
Vasopressim		Pro-opiomelanocortin	Peptidase		Memory
ACTH			Peptidase		
MSH		Pro-opiomelanocortin			Pain
Substance P		Neurokinin B gene and substance P/neurokinin A gene			
Opioid eptides:					
Enkephalins		Proenkephaline	Peptidase	Amino acids	Analgesia, Respiratory depression, Sedation, Euphoria, Constipation, Meiosis
Endorphins		Pro-opiomelanocortin	Peptidase		
Dynorphins		Prodynorphin	Peptidase		
Nitric oxide (NO)	Modulation of transmission	Arginine, O2	NO synthase	--------	Vasodilatation, Smooth muscle relaxation, Penile erection, Memory, Cerebral ischemia

Table 2: Biochemical chart and medical relevance of some major neurotransmitters

Neurotransmitter Biogenic amines	**Effect**	**Precursors or sources**	**Enzyme catalysts**	**Metabolites**	**Medical andclinical relevance**
Serotonin (5HT)	Excitatory	Tryptophan	Tryptophan Hydroxylase, 5-HT Decarboxylase	5-HIAA	Migraine, Depression, Sleep disturbance, Pain, Vomiting, Anxiety, Dementia, Overeating
Dopamine	Excitatory	Tyrosine, L-Dopa	Tyrosine Hydroxylase, L-DOPA decarboxylase	Noradrenaline	Parkinson's disease, Alzheimer's disease, Schizophrenia, Vomiting
Noradrenaline (NA) Adrenaline	Excitatory Excitatory	Tyrosine, Dopamine Tyrosine, NA	Dopamine β-hydroxylase Phenylethanolamine-N-methyltransferase	Adrenaline, Vanillylmandelate (VMA), 3,4-Dihydroxymandelic acid (DOMA), Normetanephrine (NMN), 3-Methoxy-4-hydroxyphenylglycol (MOPG)	Migraine, Mood disorders, Bladder control, Increased appetite, Sleep disorders, Cardiovascular control, Allergic reactions
Histamine	Inhibitory	Histidine	Histidine decarboxylase	-------	Vasodilatation, Ulcer, Allergic reactions, Asthma

Table 3: Biochemical chart and medical relevance of some major neurotransmitters

References:

1. Schousboe A. and Waagepetersen H S. GABA: Homeostatic and pharmacological aspects. Progress in brain research. Gaba and the Basal Ganglia - From Molecules to Systems. 2007; 160: 9-19.
2. Greengard P, Valtorta F, Czernik AJ et al. Synaptic vesicle phosphoproteins and regulation of synaptic function. *Science* AAAS. 1993; 259(5096): 780-785
3. Bajjalieh S M. **and** Scheller R H. The Biochemistry of Neurotransmitter Secretion**.** Jbc online by The American Society for Biochemistry and Molecular Biology. 1995; 270(5): 1971-74.
4. Vijayan E. Role of neurotransmitters and neuropeptides in the control of gonadotropin release: A review. Journal of biosciences. 1985;7(2): 207-213.
5. Hyman S. E. Neurotransmitters. Current biology. 2005; 15(5): R154-R158.
6. Murray R K, Granner D K, Mayes P A et al. Harper's Illustrated Biochemistry. 26th edition. Lange Medical Books/McGraw-Hill; 2003.
7. Petroff OA. "GABA and glutamate in the human brain". *Neuroscientist* 2002; **8** (6): 562–73.
8. Schousboe A, Waagepetersen H S. "GABA: homeostatic and pharmacological aspects". *Prog. Brain Res.* 2007**; 160**: 9–19.
9. Taylor C., Fricker A. D., Devi L. A et al. Mechanisms of action of antidepressants: from neurotransmitter systems to signaling pathways. Cellular Signalling. 2005; 17(5): 549-557.
10. Boon N A, Colledge N R, Walker B R et al. Davidson's Principles and Practice of Medicine. 20th edition. Churchill Livingstone, Elsevier; 2006.
11. Lodish HF, Berk A, Kaiser CA et al. Molecular Cell Biology. 6th edition. W.H. Freeman; 2007.
12. Koolman J and Roehm K H. Color Atlas of Biochemistry. 2nd edition. Thieme; 2005.
13. Gilbert H F. Basic concepts in Biochemistry- A student survival guide. 2nd edition. McGraw-Hill; 2000.
14. Murray R K, Granner D K, Mayes P A, and Rodwell V W. Harper's Biochemistry. 24th edition, Lange Medical Books; 1996.
15. Corwin E. J. Handbook of Pathophysiology. 3rd edition. Lippincott Williams and Wilkins; 2008.
16. Berg J M, Tymoczko J L, Stryer L. Biochemistry. 5th edition. W. H. Freeman and company; 2002.
17. Ghildyal P and Manchanda R**.** Neurotransmission by ATP: New insights, novel mechanisms. Indian Journal of Biochemistry and Biophysics. 2002; 39(3): 137- 47.
18. Ghildyal P, Palani D and Manchanda R. Old Molecule, New Roles: Neurotransmission by ATP. 2005
19. Ganong W F. Review of medical physiology. 22nd edition. The McGraw-Hill Companies; 2005.
20. Humeau Y, Doussau F, Grant N J et al. How botulinum and tetanus neurotoxins block neurotransmitter release. Biochimie. 2000; 82(5): 427-446.
21. Gottfries C G. Alzheimer's disease and senile dementia: Biochemical characteristics and aspects of treatment. Psychopharmacology, 1985; 86: 245-252).
22. Abi-Dargham A, Rodenhiser J, Printz D et al. From the cover: increased baseline occupancy of D2 receptors by dopamine in schizophrenia. *Proc Natl Acad Sci U S A.* 2000;97(14):8104-9.
23. Manso G. Biochemistry of neurotransmitters.2008 (The Whole Health Center • 7211 Regency Square Blvd, Suite 200 • Houston.
24. Haines D E. Fundamental neuroscience for basic and clinical applications. 3rd edition. Elsevier; 2007.