ISSN 2077-8333 (print)
ISSN 2311-4088 (online)

ЭПИЛЕПСИЯ и пароксизмальные состояния

2026 Том 18 №1

EPILEPSY AND PAROXYSMAL CONDITIONS

2026 Vol. 18 №1

https://epilepsia.su

https://doi.org/10.17749/2077-8333/epi.par.con.2026.233
ISSN 2077-8333 (print)
ISSN 2311-4088 (online)

A new twist in the story of neurochemical communication: co-transmission

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ABSTRACT

A substantial amount of progress has been made in the field of neurohumoral transmission, which has led to the disclosure of precise details regarding the communication mechanisms that occur within the neurological system. This review article gives an extensive analysis of neurohumoral transmission, focusing on the evolving concept of co-transmission and its implications for understanding psychiatric disorders in adolescents. It first provides details on classical neurotransmitters: acetylcholine, serotonin, dopamine, glutamate, and gamma-aminobutyric acid and their role in neuronal communication. Recent research findings have shown that many neurons have the ability to simultaneously release one or more than one neurotransmitter, a phenomenon termed as co-transmission and seem to add complexity to how signals are processed through the nervous system. This phenomenon raises important implications in adolescent psychiatric disorders such as depression, anxiety, schizophrenia, attention deficit hyperactivity disorder, and autism spectrum disorder, which inevitably worsen during this stage of critical development. Recent findings suggest that diminished neurotransmitter co-transmission in certain regions, such as the prefrontal cortex, might be associated with some of these impaired cognitive and emotional regulatory processes. Understanding these complex mechanisms might provide insights into the development of effective treatments targeting several neurotransmitter systems simultaneously-especially during adolescence, when the brain is particularly sensitive to chemical interactions. This review integrates recent findings into a discussion on their implications for treatment strategies, and it hints at new pharmacological interventions directed at modulating co-transmission pathways that can enhance mental health outcomes in adolescents.

KEYWORDS

neurohumoral transmission, co-transmission, classification, neurotransmitters

For citation

Narwal S., Arora S., Kumari P., Dandha T., Dhankhar S., Sharma P., Rani N. A new twist in the story of neurochemical communication: co-transmission. *Epilepsia i paroksizmal'nye sostoania / Epilepsy and Paroxysmal Conditions*. 2026; 18 (1): 48–61 (in Russ.). https://doi.org/10.17749/2077-8333/epi.par.con.2026.233.

Новый поворот в истории нейрохимической коммуникации: котрансмиссия

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РЕЗЮМЕ

В области нейрогуморальной передачи достигнут значительный прогресс, что привело к описанию неизвестных деталей процессов коммуникации, происходящих в нервной системе. В настоящем обзоре представлен подробный анализ нейрогуморальной передачи, особое внимание уделено развивающейся концепции котрансмиссии и ее значению для понимания психических расстройств у подростков. Приводятся сведения о классических нейромедиаторах (ацетилхолине, серотонине, дофамине, глутамате и гамма-аминомасляной кислоте), а также об их роли в нейронной коммуникации. Недавние исследования показали, что многие нейроны способны одновременно высвобождать один или несколько нейромедиаторов (явление, известное как котрансмиссия), что может усложнять обработку сигналов в нервной системе. Котрансмиссия имеет большое значение для развития психических расстройств у подростков, таких как депрессия, тревожность, шизофрения, синдром дефицита внимания и гиперактивности и расстройства аутистического спектра, которые неизбежно усугубляются на данном критическом этапе развития. Последние исследования показывают, что снижение котрансмиссии нейротрансмиттеров в ряде анатомических областей, таких как префронтальная кора, может быть связано с некоторыми из указанных нарушений когнитивных и эмоциональных регуляторных процессов. Понимание этих сложных механизмов будет способствовать разработке эффективных методов лечения, направленных на одновременное воздействие на несколько нейротрансмиттерных систем, особенно в подростковом возрасте, когда мозг особенно восприимчив к химическим воздействиям. В обзоре обобщены последние данные, продемонстрировано их значение для стратегий лечения, представлены новые фармакологические вмешательства, направленные на модулирование путей котрансмиссии, которые могут улучшить показатели психического здоровья у подростков.

КЛЮЧЕВЫЕ СЛОВА

нейрогуморальная передача, котрансмиссия, классификация, нейротрансмиттеры

Для цитирования

Нарвал С., Арора С., Кумари П., Дандха Т., Дханкхар С., Шарма П., Рани Н. Новый поворот в истории нейрохимической коммуникации: котрансмиссия. *Эпилепсия и пароксизмальные состояния.* 2026; 18 (1): 48–61 (на англ. яз.). https://doi.org/10.17749/2077-8333/epi.par.con.2025.233.

INTRODUCTION / ВВЕДЕНИЕ

Neurotransmitter is a kind of message carrier that transfer signals through the chemical junction, from one to another neuron. It can manage many factors like the accessibility and outlay of neurotransmitters. The liberated the standard activities The released neurotransmitter binds to receptors on the postsynaptic cell and initiates its physiological response of the postsynaptic cell and it bind, remove and deactivate the neurotransmitter by enzymes or presynaptic reabsorption. Neurotransmitter is generated, passes across the synapsis and ultimately hooks up with the receptors of the postsynaptic neurons in reply to the threshold and graded action potential [1, 2].

Due to this neurotransmitters binding, it has an inhibitory or excitatory effect on the postsynaptic neuron. The binding may cause either short-term or long-term modifications, such as the so-called postsynaptic change, which is a shift in the membrane's potential. A compound rigid neural network form from the neurons and from these channels impulses passes out. Neurons interrelate at appoints known as synapses but neurons never clutch each other [2].

Neurotransmitters release (**Fig. 1**) when an impulse comes to the synapses, which affects the other neurons and shares its information through the action potential. Excitatory and inhibitory inputs received from the neurons. Less chance exists

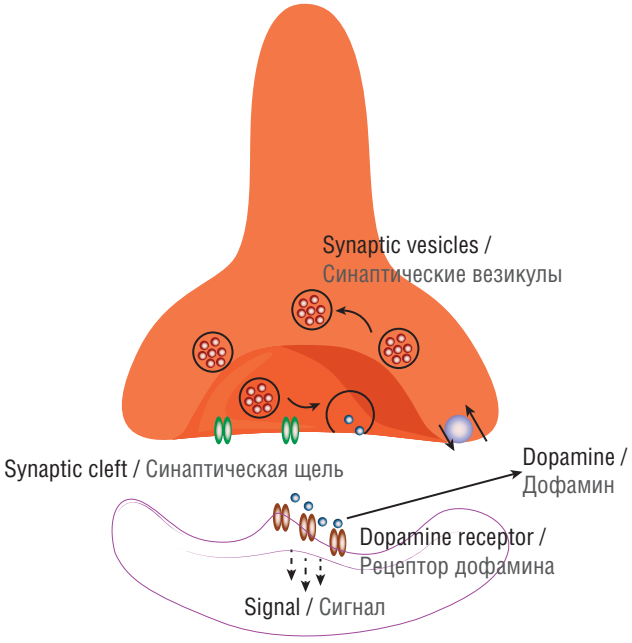


Figure 1. Neurotransmission at synaptic cleft

Рисунок 1. Нейротрансмиссия в синаптической щели

for the neuron to fire if both effects are merged into one and the neuron will be more likely to fire as a result of the overall inhibitory effect if the overall effect is excitatory [3]. The distance between the membrane potential and the threshold potential is how one would define “fire.” Because the action potential activates enough voltage-dependent sodium channels, all outward currents are increased by net inward sodium current. While inhibitory inputs guide all the neurons away from threshold, excitatory responses lead all the neurons there. Only neurons with membranes that have crossed the threshold will fire during an action potential, making it an “all-or-none” event. When the action potential is started it will grow along with the axon it leads to the liberation of neurotransmitters at the synaptic bottom. It also transfers it’s all information to the other neuron [3, 4].

A neurotransmitter is also known as the chemical messenger of the body which transfers signals sent by neurons to muscles, other neurons, or among the many neurons. In the synaptic cleft, impulses are exchanged between two neurons. The electrical signals change into the chemical signals and these rules passes along the axon [4, 5].

Independent of presynaptic action potentials, in order to release neurotransmitters in signal quanta packets, they are purposefully placed in cavities. Released neurotransmitters affect postsynaptic neurons in a micro inhibitory or micro excitatory manner. By this process the action potential compactly boost up. One of three proposed mechanisms may be used to recycle neurotransmitters that have blisters surrounding active sites [5]. Neurotransmitters mechanism is conducted in two steps:

– incomplete vesicle's opening and closure;

– membrane joining, recycling, and/or recycling into the endosome after the vesicle.

The amount of calcium in the micro kingdom is a major factor in vesicular fusion which is situated near to the calcium channels and they are allowed only for few seconds for neurotransmitter release, when it returns back to normal calcium concentration it takes more time. The target of botulinum toxins is a protein complex called SNARE (soluble N-ethylmaleimide-sensitive factor attachment receptor) that drives exocytosis [6]. When neurotransmitters liberated, it enters and come across receptor. Ionotropic and G protein-coupled receptors for neurotransmitters are possible. Only when ionised by a ligand can they be allowed to pass. The coordination of ion partiality is carried out by the several subunits that make up receptors. Metabotropic receptors are G protein-coupled receptors that undergo structural changes in response to a ligand, which slow down the intracellular response. A transporter often ends neurotransmitter action, though enzymatic inactivation is sometimes plausible [7, 8].

Each neuron receives impulses from a large number of other neurons through their attachments. These impulses are added together at the axon hillock during summation. Only after receiving an excitatory impulse will an action potential is produced. In contrast, if a neuron receives an equal number of inhibitory and inhibition counteracts the stimulation and cancels out the excitatory impulses, bringing an end to the nerve impulse. The likelihood, pattern, and postsynaptic receptor sensitization of neurotransmitter release, are intimately correlated with action potential production [9, 10].

In spatial summation, impulses are combined and then they are collected where they add up on neurons of the unlike sites, thus that even though each impulse alone wouldn't be enough to trigger firing, the neuron can activate when such impulses are received simultaneously [8].

It is possible to define temporal summation as the ability of impulses received at the same location to combine their effects if they are timed closely together. Therefore, even though each impulse would not be enough to trigger activation on its own, when multiple impulses are received, the neuron may fire [9, 11].

The chemical which behaves as neurotransmitter can be identified on the following criteria:

– it has to be made within the neuron;

– the neuron must contain the necessary precursor enzymes;

– it needs to be controllable and manageable.

Presynaptic neuron should release the chemical, which binds to receptors on the post-synaptic neuron. Numerous bodily activities are controlled by nerves and neurotransmitters [12, 13]:

– help in heartbeat and blood pressure;

– breathing;

– body muscle movements;

– retention of learning, memory;

– healing, aging and sleep;

– respond against stress;

– various body senses.

A large number of the nerve cells are present in the body. These nerve cells are consisting of [13, 14] (**Fig. 2**):

– a cell body (It is crucial for the creation of neurotransmitters and supports the maintenance of the nerve cell's numerous functions);

– axon electrical signals (are conveyed by the axons to the end point along the nerve cell);

– an axon terminal (it is a location where a chemical signal is created from an electrical message using neurotransmitters to communicate with nearby muscle, nerve, and other cell types; it is a point where neurotransmitters are situated in a part of the neurons; these are restored within thin-walled cavities known as synaptic vesicles and thousands of neurotransmitter molecules are presents in the cavities).

The electrical charge of a communication that is sent to a nerve cell first enters neurotransmitter vesicles before combining with the membrane of the nerve cell at the cell's edge.

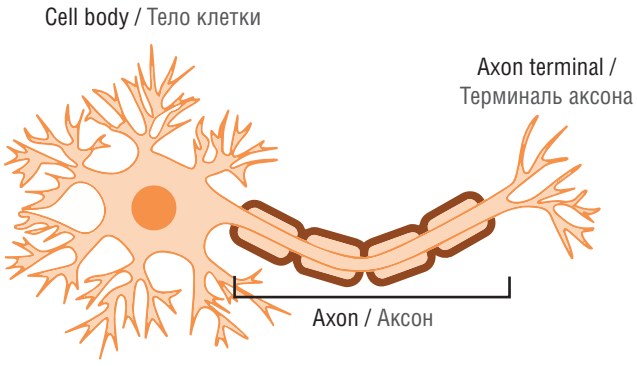


Figure 2. Structure of neuron

Рисунок 2. Строение нейрона

Messages are liberated into the fluid-filled space. These fluids filled the spaces which are known as synaptic junction. The neurotransmitters convey the communication over lower than forty nanometres wide. Every type of neurotransmitter attaches to and interacts with a specific receptor on the target cell. Similar to an electrical pulse in a different nerve cell, the target cell's change or action was then fixed by the neurotransmitter following combination. Hormones are liberated from the cell into a gland after contraction of muscle [14, 15].

On the basis of specific neurotransmitter, neurotransmitters release in three four possible steps (**Table 1**):

– excitatory (excitatory neurotransmitters mean excitation of the neuron and transmit the message; the next cell receives the message, and so forth) – e.g. epinephrine, glutamate, epinephrine, and norepinephrine [16];

– inhibitory (neurotransmitters that act as inhibitors restrict the chemical message from being transmitted further) – e.g. gamma-aminobutyric acid (GABA), glycine, and serotonin;

– modulatory (working of the chemical messengers controlled by the modulatory neurotransmitters; they modify the cells how to transfer the message at the synapse; these neurotransmitters influence many neurons at the same time) [17].

When neurotransmitters send the message, the molecules need to be separate and outside of the synaptic cleft. They will convey the message in three possible ways [17, 18]:

– by the diffusion process;

– by reuptake process when they are reabsorbed and recover by the nerve cell;

– by the degradation process (they cannot be identified because they break down in the synapsis with the help of enzymes).

MECHANISM OF ACTION OF NEUROTRANSMISSION / МЕХАНИЗМ ДЕЙСТВИЯ НЕЙРОТРАНСМИССИИ

Neurotransmitters or ligands are known as when the neurons transfer their message to the target tissues at the junction and where they liberated their chemical substances called neurotransmitters (ligands). Chemical substances transfer the messages that why it is known as chemical neurotransmission and it occurs within chemical junction [19].

Table 1. Various examples of the neurotransmitters

Таблица 1. Примеры различных нейротрансмиттеров

Neurotransmitters / Нейротрансмиттеры	Examples / Примеры
Excitatory / Возбуждающие	Glutamate / Глутамат Acetlycholine / Ацетилхолин Histamine / Гистамин Dopamine / Дофамин
Inhibitory / Тормозящие	GABA / ГАМК Serotonine / Серотонин Dopamine / Дофамин
Neurohormones / Нейрогормоны	Oxytoxin / Окситоцин Vasopressin / Вазопрессин
Neuromodulators / Нейромодуляторы	Serotonine / Серотонин Dopamine / Дофамин

Note. *GABA – gamma aminobutyric acid.*

Примечание. *ГАМК – гамма-аминомасляная кислота.*

Each junction or synapse consists of the following parts:

– presynaptic membrane (made up of presynaptic nerve fibres and the terminal bouton membrane);

– postsynaptic membrane (target cell membrane);

– synaptic cleft (the presynaptic gap is located between the postsynaptic gap and the membrane [20].

– the centre of the terminal bouton of the presynaptic nerve fibre generates and stores a large number of neurotransmitter-containing vesicles (when an action potential depolarizes the presynaptic membrane, calcium voltage-gated channels open; opening of the calcium gated channels causes calcium ions to enter the terminal bouton, where they change the state of the presynaptic membrane's membrane proteins and cause the exocytosis of the neurotransmitters in the synaptic cleft) [21, 22].

Neurotransmitters linked to postsynaptic membrane receptors as they crossed the synaptic cleft. When neurotransmitters interact to a receptor, open and shut postsynaptic membrane ligand-gated channels. Ion channels can open or close and are also known as ligand-gated channels, which alters how chloride, sodium, calcium, and potassium ions can pass through the postsynaptic membrane. This activity triggers an inhibitory or stimulatory response [23].

When a neurotransmitter induces a target cell to act and that action occurs at an excitatory synapse, that neurotransmitter is said to be an excitatory neurotransmitter. On the other hand, neurotransmitters are known as inhibitory neurotransmitters when they act in an inhibitory synapse and inhibit the target cell. As a result, the type of neurotransmitter affects the type of connection (or synapse) and how the target tissue responds [24]. Excitatory neurotransmitters cause depolarization of the postsynaptic cells and the development of an action potential. Acetylcholine (ACh) makes muscles contract more forcefully. Target cells are hyperpolarized by inhibitory synapses, which keep them far from the action potential threshold and impair their ability to function [25, 26].

For example: GABA stops the involuntary movements. The neurotransmitters which liberated in the synaptic cleft and take actions in a short period of time. These may be broken down by different enzymes like ACh esterase or recycled after being reabsorbed into the terminal bottom of the presynaptic neuron. ACh, norepinephrine, and epinephrine are the examples of those neurotransmitters which have short live but fast excitatory action on the other hand the main inhibitory neurotransmitter is GABA [27].

The structural alterations caused by repeated synaptic pursuit, such as the development of additional synapses, modifications to the dendritic tree, or axon elongation, can have long-lasting impacts on the receptor neuron. Studying repeatedly and incessantly increases the number of synapses in your brain, enabling you to recall information as needed. This is the best example of the learning process [28].

Neuro-modulators are the chemical substances that are linked with synapse. Neuro-modulation is totally different from the neurotransmission because they work on the synapse for different time. Neuro-modulators are not tumble down and reabsorb so fast by the action of enzymes. Dopamine, serotonin, ACh, histamine, and nor-epinephrine are the examples of neu-

rotransmitters. Neurohormones are the other related chemical substances; formations of these are occurring in neurons after that they are released in blood. Oxytocin and vasopressin are the hormones liberated from the hypothalamus [29].

NEUROHUMORAL TRANSMISSION / НЕЙРОГУМОРАЛЬНАЯ ПЕРЕДАЧА

Stepwise process / Поэтапный процесс

Neurohumoral transmission suggested the nerve transfer messages from a cross synapses to neuro-effector junction by announcing their chemical messages. Junctional transmissions were belief to be motorized because it likely to occur in certain areas of mammalian brain (**Fig. 3**) [30].

Sympathetic nerves worked by the release chemicals similar to adrenaline and the other scientists suggested that a chemical like muscarine let out from vagus. Another scientist uses the sequential implantation of two frog hearts to provide direct evidence of humoral transfer. Both hearts are stopped when the first heart's vagus nerves are stimulated. Vagal stimulation caused a substance to be released in the first heart, which travelled to and was retained in the second heart. ACh was characterized in 1926 (vagus stoff) after that Dale specified the parasympathomimetic. The sympathetic transmitters like noradrenaline (NA) found by Von Euler. Neurohumoral transmitters like dopamine, peptides, 5-hydroxytryptamine, glutamic acid, GABA well investigated on a day's [31, 32].

The post-junctional neurohumoral transmitters must satisfy the given standards:

– liberated in medium followed by nerve stimulation;

– it must be existed in the presynaptic neuron along with enzymes;

– its implementation must bring retaliation alike, which produced by nerve stimulation.

Stages of synapse neurotransmission:

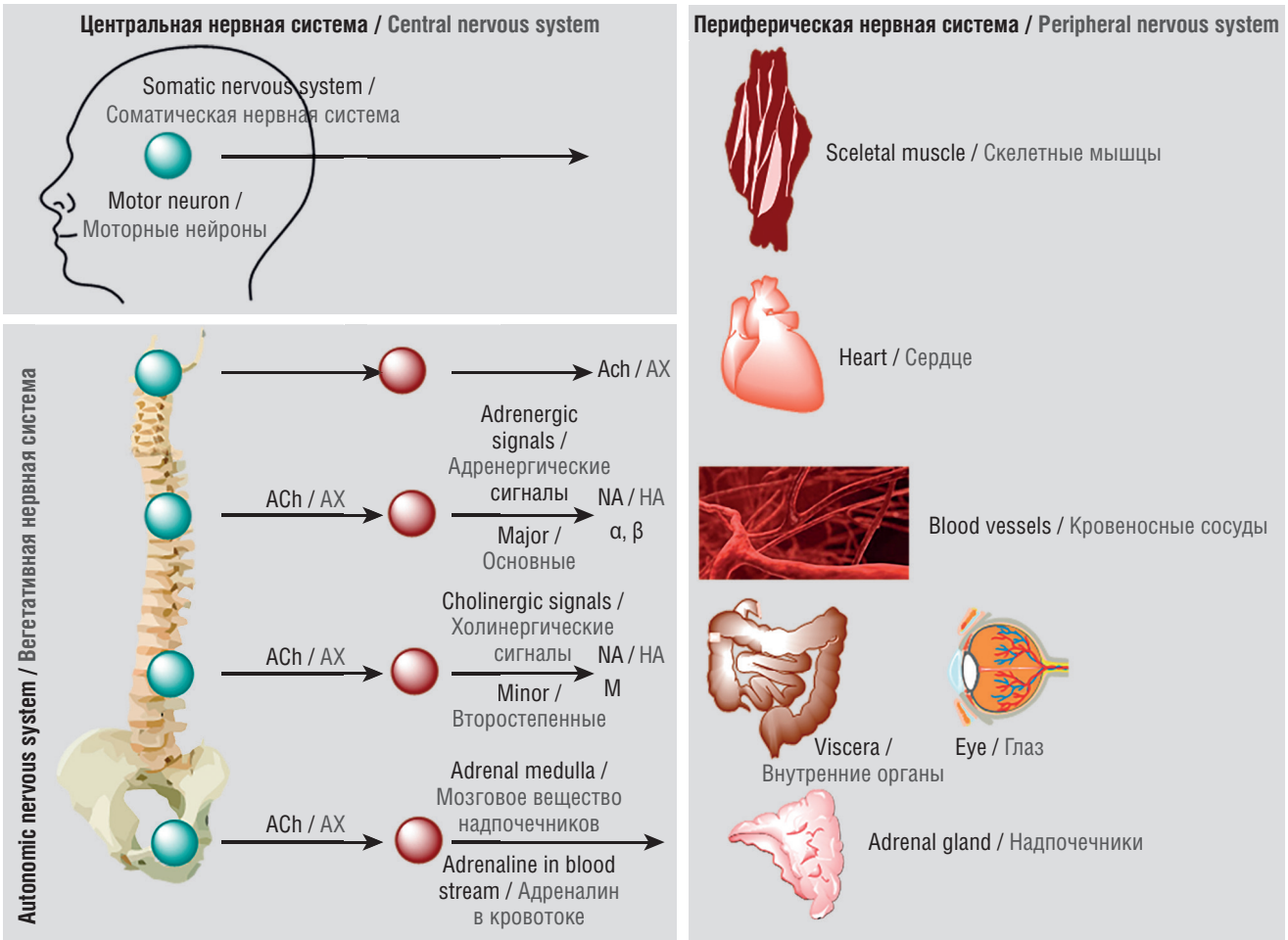
– in the initial phase, neurotransmitters are produced in the cell body, and both axon and axon terminal;

– neurotransmitters are deposited granules or vesicles in the second stage of the axon terminal;

– during an action potential calcium enters the axon terminal, due to this neurotransmitter are released into the synaptic cleft [33];

– once attached to a receptor, the transmitter operates in the postsynaptic membrane after being released;

– the neurotransmitter can be deactivated by an enzyme, returned to the terminal from whence it originated so that it can be used again, or deactivated and eliminated [34, 35].



Figire 3. Neurotransmission from central nervous system to peripheral nervous system.

ACh – acetylcholine; NA – noradrenaline

Рисунок 3. Нейротрансмиссия из центральной нервной системы в периферическую нервную систему.

АХ – ацетилхолин; НА – норадреналин

Neurohumoral transmission steps / Этапы нейрогуморальной передачи

Impulse conduction

High potassium axonal membrane penetration power, along with high axoplasmic levels of this ion and limited sodium permeability, combine to begin the resting trans membrane potential and they are actively released from the neurones. Appearance of an automatic stimulus cause a sudden rise in sodium conductance, depolarization and repolarization may be achieved by the breakdown of the potassium ions which moves towards concentration gradient. During the refractory period the distribution of the ions gets normalised by the sodium-potassium pump being turned on. The local currents circuit that drives the ionic channels at the following excitable end of the membrane is established by the action potential, which is generated without depletion. Tetrodotoxin and saxitoxin, in particular, block the rise in sodium conductance at nerve fibres and impulse conduction [36, 37].

Transmitter release

In synaptic vesicles, the excitatory and inhibitory transmitters are reserved at prejunctional nerve endings. Nerve impulse encourages the bonding of vesicular and axonal membranes by calcium entries which liquefy the membrane [37].

The transmitters, enzymes and other proteins contents of the vesicles are forced out in the end point. Numerous proteins, including synaptobrevin, synaptotagmin, syntaxin, neurexin, and synaptophysin, have been implicated in the fusion and tying up of synaptic vesicles with axonal membranes, which leads to exocytosis. By altering junctional transmission, all of these proteins function to counteract the effects of the medication. While the bulk of neurotransmitters are transported, retained, and released in synaptic vesicles through triggering exocytosis [38].

Some mediators, such as endocannabinoids and prostaglandins, are integrated when needed and diffuse and actively travel to their targets. The liberation steps can be regulated by the transmitter's their self and the regulation of the other agents by activating the specific receptors which is established on the pre-junctional membrane.eg. Release of NA is stopped by prostaglandins, dopamine, adenosine, enkephalins and while isoprenaline and angiotensin increases the release noradrenaline. Likewise, the muscarinic agonists obstruct ACh released in autonomic neuroeffector junction, but not having any effect on ganglia and skeletal muscles [38–40].

POSTJUNCTIONAL MEMBRANE TRANSMITTER / ПЕРЕДАЧА СИГНАЛА К ПОСТСИНАПТИЧЕСКОЙ МЕМБРАНЕ

It is a site on which transmitters are attached with specific receptors, its attachment depends upon on its nature. Both an excitatory (EPSP) and an inhibitory (IPSP) postsynaptic potentials are produced when it attaches (**Fig. 4**). EPSP: increase in permeability power for cations, causing sodium or calcium fluxes to be rapid or moderate, modifying the environment before potassium outflow. These ions don't move much since they flow against concentration gradients downward. IPSP: increasing the anions' penetrating strength, which causes the chloride to rise and tends to hyperpolarize the membrane. Stabilization and hyperpolarization of the membrane occur [41, 42].

Parasympathetic neuron / Парасимпатический нейрон

The key neurotransmitter ACh is speedily anatomized by particular enzyme acetylcholinesterase which is found on the synaptic membrane. Vasoactive intestinal peptide (VIP) is a common co-transmitter when released scattered slowly and degraded by the action of peptidases on different positions. It can also perform on same as well adjacent effector [43].

Sympathetic neurone / Симпатический нейрон

The main transmitter NA reclaim into the neurones by membrane vault nor-epinephrine transporter (NET) in large amount and then it reprocesses from which a small fraction diffuses out. One from this co-transmitter is neuropeptide Y (NPY) [44].

GABAergic neurone / ГАМКергический нейрон

GABA, an amino acid transmitter that is released into the synaptic cleft, is partially taken up by the GABA transporter, as well as by adjacent glial cells, and some of it dissipates through the diffusion process. Potassium ions that carry positive charges become more permeable. The basal transmitter release also had a trophic influence on the joint shape and functional condition [45].

Postjunctional activity / Постсинаптическая активность

Postjunctional action potential produces by a supra threshold Excitatory Postsynaptic Potential EPSP, which produces a nerve impulse, contraction, secretion in neurone, muscle and in glands respectively. An IPSP balance the post junctional and counter depolarized stimulus.

Termination of transmitter action / Прекращение работы транмиттера

In Figures 2, 3, the mechanism of transmitter action degradation is depicted. After fusing with the receptors, the transmitter is either locally or disproportionally destroyed. For this reason, specific carrier proteins on the axonal membrane are visible, like serotonin transporter, NET, and dopamine transporter. The pace at which transmitter action terminates is powered by the rate (1 to 1000/sec) at which replies can be transferred across a junction. Although peptide neurotransmitters like VIP, NPY, and enkephalins are not actively reabsorbed, amino acid transmitters like glutamate and gaba are to some extent taken back by movement into neuronal and nearby glial cells [44, 46]. They disperse and are exhausted by peptidases in various locations.

Co-transmission / Котрансмиссия

Co-transmission (one neurone – one transmitter model) is on the top abbreviation now days. More than one active substance is encouraged by Peripheral as well as central neurons. In the Autonomic nervous system, the chief transmitters like ACh and nor-adrenaline are the bases to detail purines (ade-

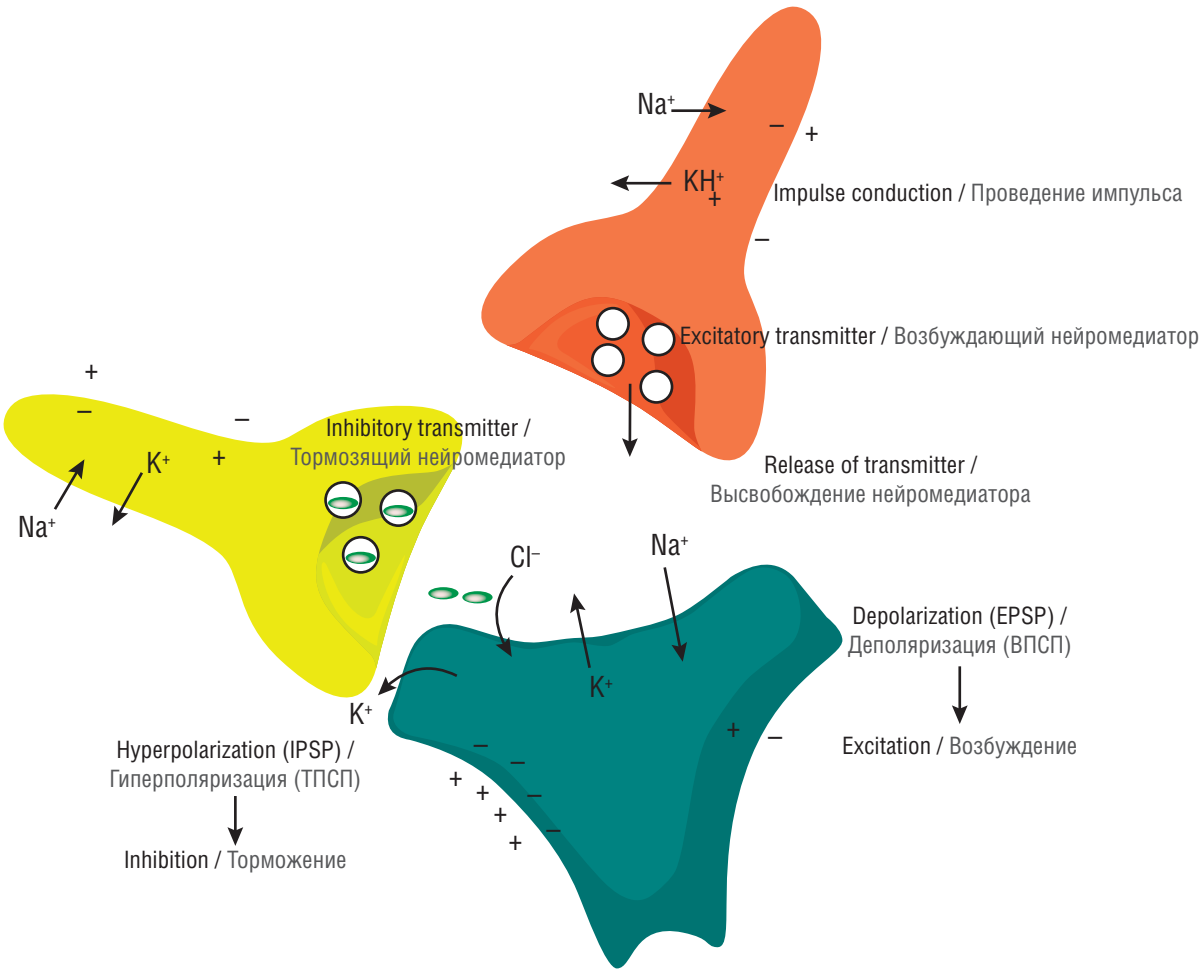


Figure 4. Neurohumoral transmission (excitatory and inhibitory effects).
IPSP – inhibitory post synaptic potential; EPSP – excitatory post synaptic potential

Рисунок 4. Нейрогуморальная передача (возбуждающие и тормозящие эффекты).
ТПСП – тормозящий постсинаптический потенциал; ВПСП – возбуждающий постсинаптический потенциал

nosine triphosphate (ATP) / adenosine), peptides, nitric oxide (NO) and prostaglandins as co-transmitters. In all almost autonomic cholinergic neurons like VIP is corelated with ACh, while ATP is related with couple of ACh and NA. The NO transmitter is present at some parasympathetic sites, so it is known as nitrergic nerves. Vascular adrenergic nerves that have NPY are the sources of enduring vessels narrowing [47].

The co-transmitters keep in the identical neurons but in dissimilar positions as shown in figure below. ATP which is set aside with non-adrenaline in the identical vesicles, after released by the nerve incitement, the additionally, co-transmitters affect the main transmitter's presynaptic break or its postsynaptic sensitivity also the co-transmitters. The key transmitter and the co-transmitter are reserved in separate vesicles at the pre-junctional nerve end, even if they occasionally share the same vesicle. Nerve impulses liberated from both the transmitters together, the co-transmitters modify acceptability of the effector for the basic transmitter or substitutes while acting on its own receptors for it. Co-transmitter may also affect pre-junctional receptors, altering how the transmitters are released. Release of the non-cholinergic non-adrenergic, transmission have been shown in various systems like autonomic innervation of the gut, salivary glands, urinary tract, vas deferens and fixed blood vessels, where nerve stimulation is skilled to conjure up the specified reaction even in residence of total adrenergic and cholinergic barricade. for instance, in a biphasic contractile response, the first and second phases are, respectively, controlled by ATP and noradrenaline receptors, and this example is effectively illustrated by activating the vas deferens of the Guinea pig with sympathetic nerves. The key transmitter and the co-transmitter are usually dissimilar in their action. The co-transmitter VIP of parasympathetic neurons give rise to moderate or lengthy running action while different one now has middle hence forth action between VIP and ACh. Similar to how co-transmitters NPY and ATP function quicker and slower than NA in sympathetic neurons, respectively [48, 49]. As well as co-transmitters like NO/VIP/NPY liberated in large region and can work on receptors at a bit distance from the site of liberation.

Co-transmitter categorized neurons. For instance, opioid peptides or substance P are used by striatal “GABAergic neurons” as their main co-transmitter.

At the same time, minimum two neurotransmitters released from the neurons. When inhibitory interneurons are absent, the other functions as a co-transmitter to provide the stabilising negative feedback required for meaningful learning. Examples

include GABA-glycine co-release, dopamine-glutamate co-release, acetylcholine (Ach)-glutamate co-release, ACh- VIP, ACh-calcitonin gene-related peptide, and glutamate-dynorphin co-release (in the hippocampal region) [50].

Both ATP and NA are sympathetic co-transmitters. Anandamide and WIN 55,212-2, two endocannabinoids, can alter how the sympathetic nervous system reacts to stimulation, which suggests that pre-junctional CB1 receptors are the mechanism by which the sympatho-inhibitory action is conveyed. Cannabinoids inhibit the sympathetic neurotransmission's noradrenergic and purinergic components [51].

Excitatory neurotransmitters / Возбуждающие нейромедиаторы

A neuron's propensity to produce an action potential is increased by excitatory neurotransmitters. Glutamate is the principal excitatory neurotransmitter in the central nervous system, while norepinephrine and epinephrine are involved in arousal and alertness mechanisms. The major neurotransmitters along with their general functions are summarized in **Table 2**. Excitatory neurotransmitters are divided into two categories: both norepinephrine and epinephrine.

Inhibitory neurotransmitters / Тормозящие нейромедиаторы

Inhibitory neurotransmitters are type of neurons this affects the neurons and decreases the likelihood of an action potential being fired by the neuron. Serotonin and GABA are two examples of inhibitory neurotransmitters [52]. These neurotransmitters and their functional roles are presented in Table 2.

Modulatory neurotransmitters / Модулирующие нейромедиаторы

Neurotransmitters are affected by modulatory neurotransmitters at the same time. Other chemical messengers are affected by modulatory neurotransmitter. Dopamine and acetylcholine are examples of neurotransmitters with modulatory functions in neural circuits.

There are at minimum 100 neurotransmitters and they can be classified according to their chemical nature (**Table 3**).

Amino acid neurotransmitters / Аминокислотные нейромедиаторы

Most of your nervous system's processes require these neurotransmitters.

Glutamate

The most common excitatory neurotransmitter is glutamate. Many sensory pathways release glutamate in their neurons, and these routes invade the cerebral cortex and the brain and spinal cord. Glutamate plays a part in learning and memory as well as the regulation of the excitability of the central nervous system as a whole. Thus, epilepsy as well as cognitive and affective disorders is linked to glutamate neurotransmission. It regulates brain activity in conditions like Alzheimer's disease, dementia, Parkinson's disease, and seizures [53].

Table 2. Neurotransmitters with structure and function

Таблица 2. Нейротрансмиттеры: структура и функции

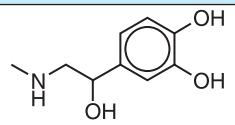
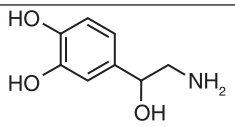
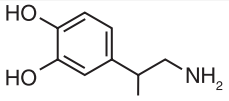
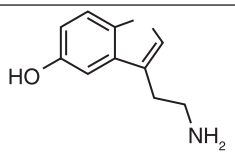
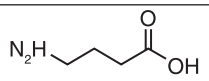
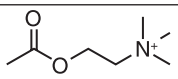
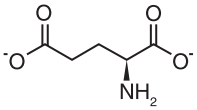
Neurotransmitter / Нейротрансмиттер	Structure / Структура	Function / Функция
Adrenaline / Адреналин		Fight / Реакция на опасность
Noradrenaline / Норадреналин		Concentration / Концентрация
Dopamine / Дофамин		Pleasure / Удовольствие
Serotonin / Серотонин		Mood / Настроение
Gamma-aminobutyric acid / Гамма-аминомасляная кислота		Calming / Успокоение
Acetylcholine / Ацетилхолин		Learning / Обучение
Glutamate / Глутамат		Memory / Память
Endorphins / Эндорфины	–	Euphoria / Эйфория

Table 3. Types of neurotransmitters according to their chemical nature

Таблица 3. Типы нейротрансмиттеров по их химической природе

Type / Тип	Examples / Примеры
Amino acids / Аминокислоты	GABA / ГАМК Glutamate / Глутамат
Peptides / Пептиды	Oxytocin / Окситоцин Endorphins / Эндорфины
Monoamines / Моноамины	Epinephrine / Эпинефрин Norepinephrine / Норапинефрин Histamine / Гистамин Dopamine / Дофамин Serotonin / Серотонин
Purines / Пурины	Adenosine / Аденозин Adenosine triphosphate / Аденозинтрифосфат
Gasotransmitters / Газотрансмиттеры	Nitric oxide / Оксид азота Carbon monoxide / Оксид углерода
Acetylcholine / Ацетилхолин	Acetylcholine / Ацетилхолин

Note. *GABA – gamma aminobutyric acid.*

Примечание. *ГАМК – гамма-аминомасляная кислота.*

Gamma-aminobutryic acid

Neurons in the cerebral cortex, basal ganglia, spinal cord, and many different areas of the cerebellum all produce GABA. GABA is the strongest neurotransmitter that acts as an inhibitor. GABA was made by glutamate. GABA, an inhibitory neurotransmitter, uplifts mood and feelings. When distributed throughout the brain, it reduces neuronal excitability throughout the entire nervous system. Lack of GABA contributes to the emergence of sadness, focus, sleep, convulsions, and anxiety [54].

Glycine

Glycine, an inhibitory neurotransmitter, is found in the spinal cord. Glycine regulates pain transmission, metabolism and hearing processing.

Monoamine neurotransmitters

Neurotransmitters called monoamines control consciousness, cognition, attention, and emotion. Due to abnormalities of monoamine neurotransmitters many diseases are occurred.

Serotonin (5-hydroxytryptamine)

Serotonin regulates emotion and mood. The brainstem's neurons produced serotonin, which stimulates the digestive system (enteric nervous system). Serotonin, which is found in the platelets, was released during the process of coagulation. Serotonin plays a key role in controlling body temperature, sleep patterns, pain perception, and mood. Reduced immune system performance, a variety of emotional diseases like depression, issues with impulse control, and even suicidal thoughts may be brought on by a lack of serotonin production. It play an important role in regulation of mood, pain, anxiety, sleep patterns, sexuality, and appetite [54].

Histamine (excitatory neurotransmitter)

Number of functions is performed by excitatory neurotransmitter in both in the peripheral nervous system (nerves that branch from the CNS) and the central nervous system (brain and spinal cord). In the blood, cells of the stomach mucosa, mast cells, and basophils are produced by neurons of the hypothalamus. Histamine is most recognised for its arousal-inducing properties, feeding behaviour and motivation. Histamine may helps in the regulation of asthma, bronchospasm, mucosal edema [52, 53].

Dopamine

Dopamine is created by substantia nigra neurons. Depending on the type of receptor that binds to dopamine, it can have both an excitatory and an inhibitory impact. Dopamine inhibits superfluous movement, which is a key factor in movement coordination. Dopamine increases growth hormone secretion in the pituitary gland. It supports obtaining increased arousal, regulating pleasure, and learning. The impacts on focus, concentration, memory, sleep, mood, and motivation are its most well-known features. Parkinson's disease, bipolar disorder, schizophrenia, attention deficit hyperactivity disorder (ADHD), and restless legs syndrome are among the illnesses associated with a deficiency of dopamine [51, 52].

Epinephrine

An excitatory neurotransmitter is epinephrine. The chromaffin cells of the adrenal gland release epinephrine. It also goes by the name of adrenaline. It triggers the “fight-or-flight” response in your body, which is what causes stress and panic. When someone experiences fear or fury, epinephrine stimulates a physical response. Epinephrine is released in large quantities into the bloodstream. Epinephrine activation increases blood pressure, heart rate, and the liver's ability to release glucose (through glycogenolysis). An increase in epinephrine levels is associated with high blood pressure, diabetes, heart disease, and other health problems [53, 54].

Norepinephrine

Norepinephrine, is another name for noradrenaline A neurotransmitter that causes excitement, it. It enters the bloodstream after being secreted by the brainstem, hypothalamus, and adrenal glands. The majority of postganglionic sympathetic nerves produce norepinephrine, which has the most well-known effects of raising alertness levels in the brain and is crucial for maintaining wakefulness in the body. It stimulates the body's natural activities. It is crucial for the endogenous epinephrine synthesis, for instance. Norepinephrine is used to treat mood disorders like sadness and anxiety, in which case the body's normal level of norepinephrine is abnormally low. Alternately, a high level of it may interfere with the sleep cycle. Norepinephrine increases blood pressure and heart rate. It helps in focus alertness, decision-making and attention [44, 46].

Peptide neurotransmitters

Polymeric amino acid chains make up peptides.

Endorphins

Endorphins function as a natural analgesic. The perception of pain is aided by endorphins. Endorphin stimulation both lessens pain and produces "feel good" emotions. Some types

of headaches and fibromyalgia may be caused by low endorphin levels [42].

Acetylcholine

In the autonomic nervous system, ACh is produced by most neurons. It aids in controlling gastrointestinal motility, blood pressure, and heart rate. ACh has a major impact on muscle contraction, memory, motivation, sexual desire, sleep, and learning. A low ACh level can lead to health problems like Alzheimer's, seizures, and muscle spasms.

Serotonin

Serotonin, for example, is deeply implicated in mood regulation and derangements in serotonin levels have been associated with depression and anxiety disorders for decades, and especially among adolescents. Dopamine is another classical neurotransmitter essential in any reward processing and motivation. The disorder that conditions interrupt dopaminergic pathways are very close to ADHD or substance use disorders and affect adolescent populations at a drastically high rate. Understanding the roles these neurotransmitters play provides foundational insight into psychiatric disorders but inevitably leads to more complex mechanisms like co-transmission. Co-transmission is the simultaneous release of more than one neurotransmitter from a neuron that could bind to different receptors or subcellular compartments within the cell. It has revolutionized synaptic communication because it is flexible and context-dependent, far more flexible than anyone had thought up to this point. This should be of considerable interest for psychiatric disorders, especially in adolescence when their brain and our youth are changing rapidly.

Adolescence is the stage that coincides with a very crucial period of neural development, which is largely characterized by maturation and refinement of synaptic connections, myelination, and improved maturity of the prefrontal cortex. Due to these changes, interaction with changes in hormones in the adolescent population makes the adolescents more vulnerable to psychiatric conditions like depression, anxiety, schizophrenia, and bipolar disorder. In this regard, co-transmission mechanisms may play an important role in providing a better insight into why some individuals may be at an increased risk of such conditions during adolescence. It could relate to glutamate and dopamine co-release in the prefrontal cortex to explain all the cognitive and emotional dysregulation observed in schizophrenia and bipolar disorder, for instance. Glutamate, being the primary excitatory neurotransmitter in the brain, plays a role in synaptic plasticity and cognitive function. Glutamate released with dopamine may modulate emotional responses and decision making that are deficient in psychiatric disorders among adolescents. This co-transmission pathway may thus be associated with the onset time of such conditions during adolescence when the brain is developmentally immature.

In addition, serotonin and substance P is an example of co-transmission of neurotransmitters. This co-transmission has been studied in anxiety and stress-related disorders. Substance P is a neuropeptide that plays a role in pain sensation and stress. Co-released with serotonin, it might modify the response of the body to stress or inhibit emotional regulation; therefore, adolescents who are under highly stressful academic, social, or familial pressures might be specially vulnerable to impairments in co-transmission and anxiety disorders. This flexibility of co-transmission enables the nervous system to fine-tune its responses to a wide range of internal and external stimuli. In adolescents, whose neural circuits are still maturing, it can be both beneficial and detrimental in that this flexibility, on the one hand can be helpful, and on the other hand it becomes a double-edged sword, allowing greater adaptability to changes occurring in the environment, which are crucial at this transitional stage of life. On the other hand, if these mechanisms of co-transmission are dysregulated, they may lead to the development of psychiatric diseases. For instance, the co-release of the transmitter systems GABA and serotonin in the hippocampus, a region important in memory and emotional processing, is assumed to play a role in pathology of major depressive disorder. The hippocampus is known to be particularly susceptible to reorganization and remodeling during adolescence. Disruptions in GABA-serotonin co-transmission may, therefore, make patients more susceptible to impairments in emotional regulation, possibly to depression. Even though these specific systems of neurotransmission provide a foundation for consideration, there also exists a more general neurodevelopmental disorder context to which these discussions are germane during adolescence. Indeed, mechanisms that involve co-transmission might play a role in two other such disorders: autism spectrum disorder (ASD) and ADHD. For example, such co-release abnormalities of dopamine and ACh in the striatum might therefore contribute to characteristic behavioral and attentional challenges of ADHD.

A region implicated in many disturbances of ADHD is the striatum, which plays a critical role in motor regulation and reward processing. Co-transmission within this region may therefore change how adolescents with ADHD handle reward processing and make decisions that underlie impulsivity and inattention. Imbalance in excitatory vs inhibitory neurotransmission as it relates to ASD although the pathophysiology underlying ASD is not known, hypothesized disturbances in both excitatory and inhibitory neurotransmission have been considered such an underlying mechanism. The disturbance could be in co-transmission of GABA and glutamate in the prefrontal cortex and other brain regions that are implicated in social cognition for individuals with ASD. Such an imbalance can explain difficulties with social communication and the presence of repetitive behaviors characteristic of the disorder. It would probably be a difficult period for most adolescents with ASD, as changes in the brain enhance these imbalances in co-transmission at the overall level.

Even though the classical model of neurotransmission provided much answer to psychiatric disorders, co-transmission could be better needed for understanding the neural processes in action. Perhaps, by accepting that even one neuron can stimulate the release of multiple neurotransmitters at the same time, there is a greater appreciation for the complexity of neural signaling and its behavior-related implications. This happens during a very crucial time in life: the adolescent years, when many develop from strong periods of change in both their neural structures and psychology. Perhaps it is through co-transmission mechanisms that some psychiatric conditions have become so prominent in the adolescent years, and

perhaps it is through these mechanisms that they may be dealt with more effectively. For example, pharmacological treatments targeting pathways of co-transmission may open new avenues for treating psychiatric conditions in young individuals.

Drugs modifying the co-release of serotonin and dopamine may thus offer more precise treatments for mood disorders such as depression and bipolar disorder. Also, therapies aimed at the glutamate-GABA co-transmission imbalance may find their application in the effective treatment of schizophrenia and ASD, holding possible hope for adolescents suffering from these devastating conditions. There has been a spate of research lately on co-released neurotransmitters, such as glutamate and dopamine, which have an important role to play especially in those parts of the brain that are subject to critical development during adolescence, like the prefrontal cortex and the striatum. The prefrontal cortex is one of the very busy parts of the brain involved in decision making, emotional regulation, and the inhibition of impulses. It is hugely maturing during adolescence.

D. Eskenazi et al. (2021) in a study on co-transmission in the same region, suggest that changes in glutamate and dopamine co-release may be a direct contributor to cognitive-emotional dysregulation, which is observed in some conditions: schizophrenia and bipolar disorder [55]. This, therefore, as a general observation, translates to a concept where such alterations in co-transmission during such a phase of life lead to psychiatric symptoms in adolescents. The results of this study have deep implications in the understanding of the development path of psychiatric conditions. Schizophrenia has traditionally been thought of in terms of aberrant dopamine transmission, and yet recent evidence indicates that glutamatergic dysfunction also plays an equally crucial role in its pathology. This co-release of neurotransmitters could explain the contradictory nature of symptoms of schizophrenia: positive symptoms include hallucinations and delusions, whereas negative symptoms include cognitive deficits and emotional flatness. Thus, adolescents who present with early markers of schizophrenia may experience disturbances in co-transmission processes that impact both cognition and emotions. The new lines of treatments emerging today come under pharmacological interventions meant to correct disturbances in both glutamate and dopamine imbalances, suggesting that their therapeutic options might be much better for adolescents at risk. Furthermore, co-transmission that is mediated by serotonin as well as substance P has been implicated in modulation of mood as well as anxiety, particularly during periods of stress.

A. Markiewicz-Gospodarek et al. (2022) attempted to examine the engagement of serotonin and neuropeptide co-release in models of animals and found out that impairments of this system may enhance anxiety responses, especially at puberty, when levels of stress increase with both environmental and developmental events [56]. This supports the suggestion that psychopathology, such as generalized anxiety disorder or PTSD, arising from stress could be due to an imbalance in these systems' co-transmission. Clinically, this suggests that therapies impacting both serotonin and neuropeptide systems could have better efficacy in the management of anxiety disorders in adolescents. With regard to ADHD, further understanding has also occurred concerning its relationship with mechanisms of co-transmission. Recently, a study was published on ADHD that listened in on how the co-release of dopamine and ACh in the striatum in humans with ADHD resulted in a disrupted system; it explained how the imbalance of neurotransmitter systems involving adolescents with ADHD explained why, for instance, they typically cannot pay attention, be motivated, or exert impulse control. This discovery may suggest that drugs modifying dopamine pathways-the most commonly used drugs currently, including psychostimulants-had not resolved the underlying pathology but only partially relieved it.

Perhaps, a more subtle treatment approach that includes ACh transmission could further enhance outcomes for such patients. Another critical focus of research is ASD. This is achieved through the modulation of excitatory (glutamate) versus inhibitory (GABA) neurotransmission by co-transmission in the brain regions involved in social cognition, among them the prefrontal cortex and amygdala. V. Hollestein et al. (2023) posited that disturbances in co-transmission in these areas of the brain might be part of the disorders present in adolescent ASD individuals characterized by social and communicative impairments [57]. This research holds crucial implications, because it points out that the treatments aimed at rebalancing excitatory to inhibitory neurotransmission are likely uniquely beneficial in core ASD symptoms.

The interventions regarding pathways of co-transmission for adolescents with ASD may thus offer an even more targeted approach to therapy than traditional behavioral treatments provide [55–57].

Despite such exciting advances, challenges in translating such findings into clinical practice are enormous and critical. One challenge is the system itself – the co-transmission systems are so complex. Researchers are only now starting to put together how glutamate, dopamine, serotonin, and other such neurotransmitters talk to each other in the brain. These systems are highly context-dependent and could have widely different effects based on the brain region, receptor type, and even genetic or developmental variations across individuals. It is this variation that leaves it challenging to have one treatment, which fits all adolescents with the rapidly changing brains. Another limitation in many of the findings of disruption in co-transmission is that very few of them have led to particular pharmacological treatments used for the adolescents. Most of the medications such as selective serotonin reuptake inhibitors or dopamine agonists still remain as targets singular neurotransmitter systems and do not address the complexity of co-transmission.

This thus calls for the need for future research into developing multi-target drugs that can modulate multiple neurotransmitter systems at once, thereby leading to a more holistic approach in treatment. There also is an ethical dimension to consider, particularly when treating adolescents: their brains are still developing, so there could be longterm positive and negative effects of altering neurotransmitter systems pharmacologically. Of course, longitudinal studies will be needed to evaluate the impact of targeting pathways during co-transmission through adolescence, ensuring not only that the symptoms go away, but healthy neural development ensues in the long term [34, 35].

CONCLUSION / ЗАКЛЮЧЕНИЕ

In this, we talked about the classification of neurohumoral transmission. Although there are different types of neurons present in our nervous system, we are only talking about the essential ones like ACh and dopamine. We also know what happens in neurohumoral transmission and how we receive messages impulsively. Once released, a neurotransmitter enters the synapse and encounters receptors. Neurotransmitter receptors can either be ionotropic or g protein coupled. Ionotropic receptors allow for ions to pass through when agonized by a ligand. The main model involves a receptor composed of multiple subunits that allow for coordination of ion preference. G protein coupled receptors, also called metabotropic receptors, when bound to by a ligand undergo conformational changes yielding in intracellular response. As the autonomic nervous system is a visceral efferent system, it can send motor impulses to the visceral organs. This nervous system consists of innervated smooth muscles, cardiac muscles, and glands that work automatically and constantly without conscious effort.

ARTICLE INFORMATION	ИНФОРМАЦИЯ О СТАТЬЕ
Received: 20.01.2025 **Revision received:** 26.02.2026 **Accepted:** 17.03.2026 **Published:** 30.03.2026	**Поступила:** 20.01.2025 **В доработанном виде:** 26.02.2026 **Принята к печати:** 17.03.2026 **Опубликована:** 30.03.2026
Authors' contribution	**Вклад авторов**
All authors participated equally in the collection, analysis and interpretation of the data. All authors have read and approved the final version of the manuscript	Все авторы принимали равное участие в сборе, анализе и интерпретации данных. Все авторы прочитали и утвердили окончательный вариант рукописи
Conflict of interests	**Конфликт интересов**
The authors declare no conflict of interests	Авторы заявляют об отсутствии конфликта интересов
Funding	**Финансирование**
The authors declare no funding	Авторы заявляют об отсутствии финансовой поддержки
Ethics declarations	**Этические аспекты**
Not applicable	Неприменимо
Publisher's note	**Комментарий издателя**
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