Al-Kunooze Scientific Journal

e-ISSN: 2706-6223

P-ISSN: 2706-6231

https://www.asj.kunoozu.edu.iq/

2026, 12(2):157-167

Neurotransmitters, the Chemical Messages of the Brain, Rules and Mechanisms, A Review

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Abstract

The human brain contains an estimated 86 billion neurons. Those billions of brain cells communicate by passing chemical messages at the synapse, the small gap between cells, in a process called neurotransmission. Those chemical messages are unique molecules called neurotransmitters. There are many types of neurotransmitters in the brain. But they do have a few things in common: neurotransmitters are endogenous or produced inside the neuron itself. When a cell is activated, these neurochemicals are released into the synapse from specialized pouches clustered near the cell membrane called synaptic vesicles. Specific receptors on neighboring cells can then take up the neurotransmitters, which can increase or decrease the signal being passed along a particular circuit.

Key Words: Neurotransmitters, Chemical Messages, Brain.

Introduction

Neurotransmitters : is a substance relesed from the axon terminal of the neuron which bind to the receptor and preduce physiological response. response.1–5 In the early years of the 20th century the neural basis of neurotransmitterswas discovered. During the period, The function of acetylcholine (ACh) and adrenaline were relized,The oldest known neurotransmitters.[1]

Neurotransmitters are endogenous chemicals that allow neurons to communicate with each other throughout the body. They enable the brain to provide a variety of functions through the process of chemical synaptic transmission. These endogenous chemicals are integral in shaping everyday life and functions.[2]

Chemical synaptic transmission primarily through the release of neurotransmitters from presynaptic neural cellsto postsynaptic receptors. Alterations in the levels of specific neurotransmitters have been observed in various neurological disorders, including Parkinson disease, schizophrenia, depression, and Alzheimer disease.[3]

Otto Loewi discovered the first neurotransmitters in 1926 when he

Published by: Al-Kunooze University, Basrah, Iraq

demonstrated that acetylcholine carried a chemical signal from the vagus nerve to the heart that slowed the cardiac rhythm.[4]

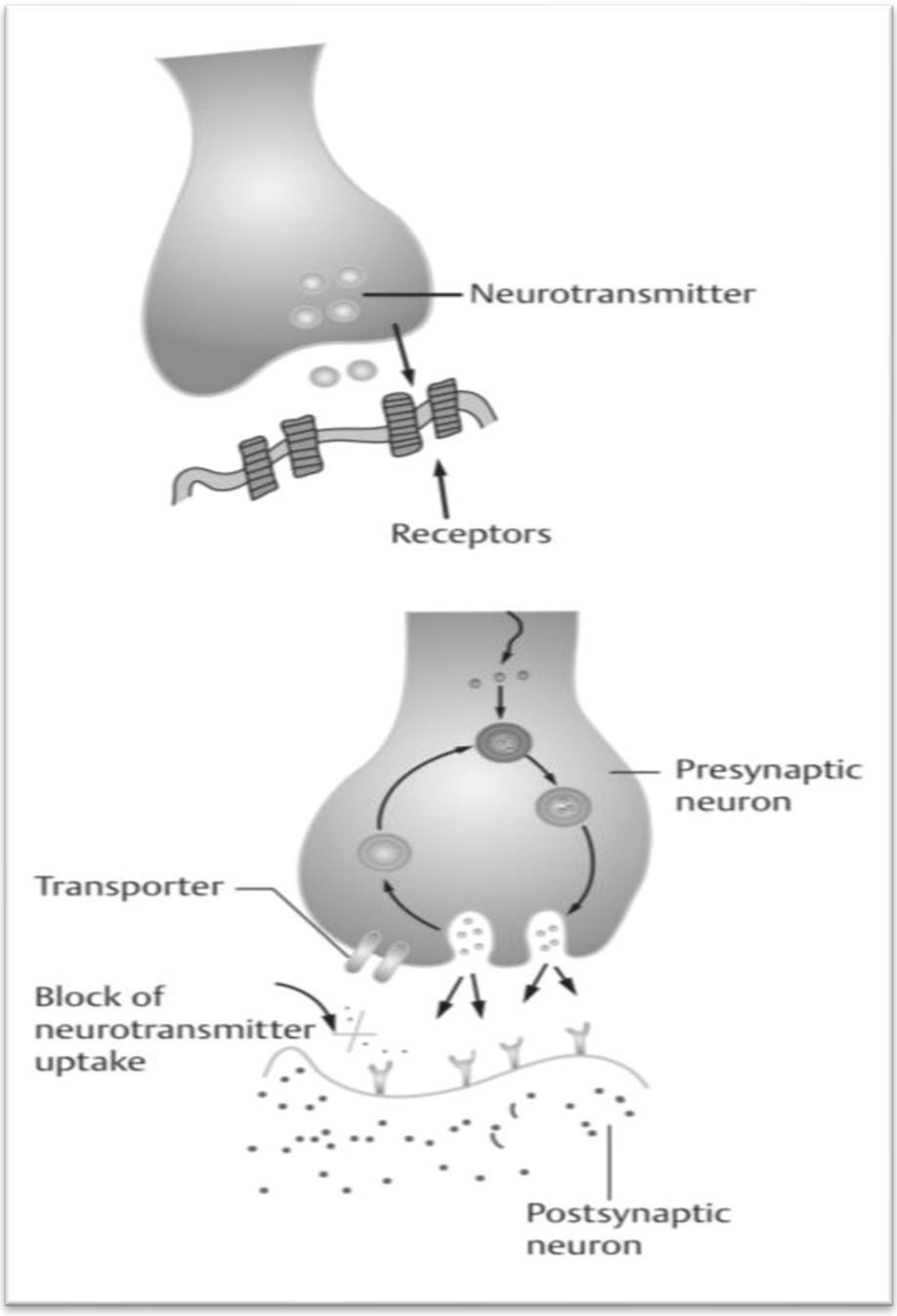

Fig. 1 The transmission of a message across the synapse occurs by chemical means. Neurotransmitters are chemicals that travel across the synapse and allow communication between neurons via the receptors that are present on the postsynaptic membranes. Neurons in the brain can have thousands of synapses (Eccles,1990).

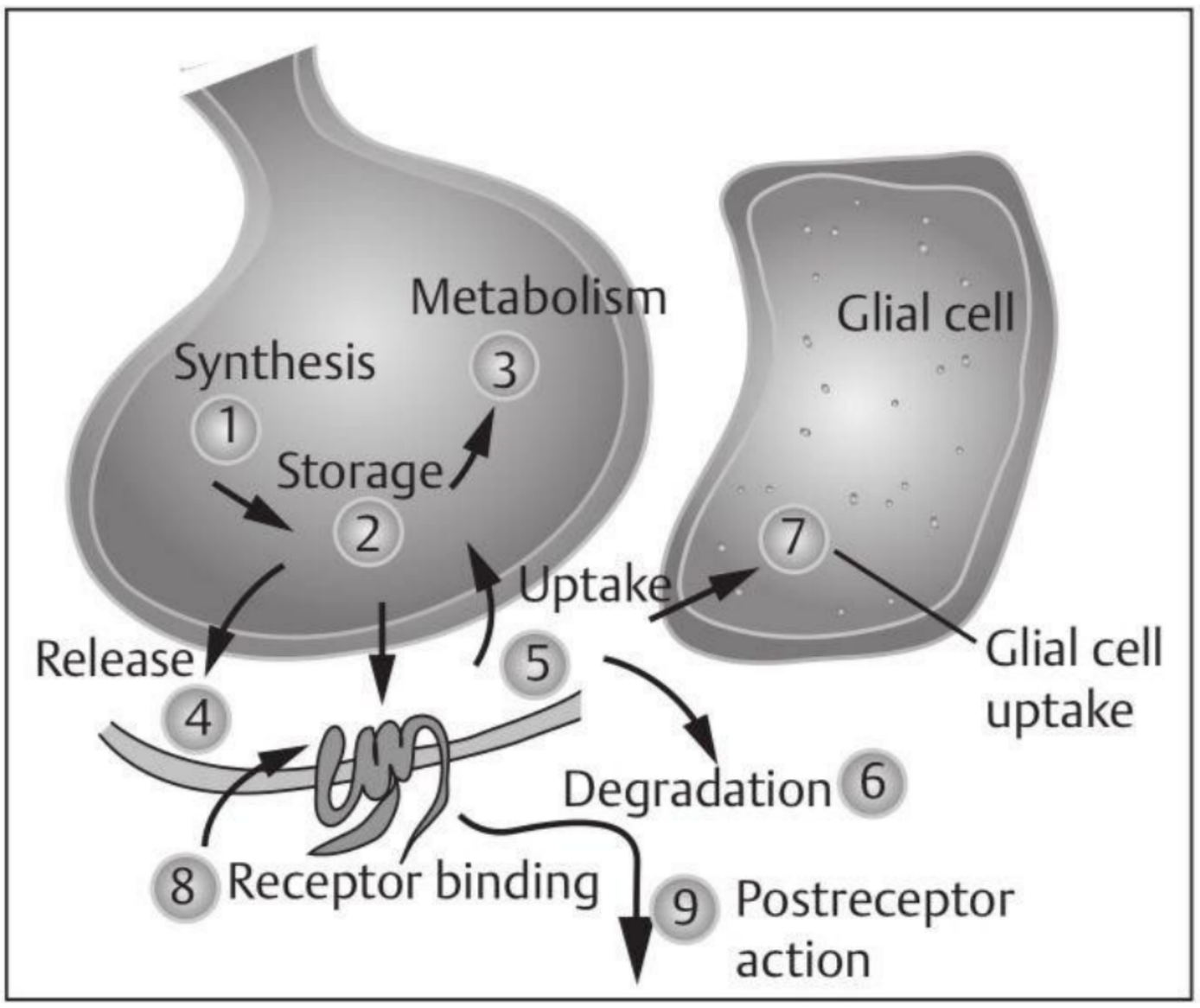

Fig. 2 Neurotransmitters released into the synapse cleft do not remain there and are subject to either inactivation or reuptake by presynaptic neurons. Reuptake refers to when the presynaptic neuron takes up most of the neurotransmitter molecules intact and reuses them again for synaptic action. Transporters present presynaptically are special membrane proteins that facilitate the reuptake process. For example, serotonin is taken back up into the presynaptic terminals and is stored for future action. Commonly used antidepressants like selective serotonin reuptake inhibitors (SSRIs) block the reuptake process (Eccles,1990).

Development:

Neurotransmitters are involved in the processes of early human development, including neurotransmission, differentiation, the growth of neurons, and the development of neural circuitry. Certain neurotransmitters may appear at different points of development. For example, monoamines are present before the neurons are differentiated. Norepinephrine levels are high in the notochord, even in the very early stages of the embryo. Serotonin has a role in morphogenesis. Excitatory amino acids tend to appear later in ontogenesis. The levels of neurotransmitters and neuromodulators tend to increase as new synapses form. Others will appearin the perinatal period, like glutamate, and plateau afterward. Hypoxia and drug-exposure can disturb the formation of neuronal circuity, leading to long-term deleterious effect in the body [5].

Function:

There are a number of neurotransmitters used by the body for different functions, including acetylcholine, glutamate,Aspartate, GABA,

glycine, dopamine, norepinephrine, and serotonin. Glutamate is the principal excitatory neurotransmitter used in the brain. It is also the primary mediator of nervous system plasticity. [6]

Aspartate is abundant neurotransmitters found in cerebral cortex ,spinal cord ,Glycine and Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitters of the brain and spinal cord.Which found in interneurons of spinal cord(Renshaw cell). [6]

account for approximately 40% of the inhibitory processing in the brain. [6]

Dopamine, another major neurotransmitter, plays an essential role in several brain functions, including learning, motor control, reward, emotion, and executive functions. Dopamine has also been implicated in psychiatric and neurological disorders. [7]

Serotonin is a neurotransmitter that modulates multiple neuropsychological processes and neural activity — many drugs used in psychiatry and neurology target serotonin. Serotonin also has implications that affect gastrointestinal processes like bowel motility, bladder control, and cardiovascular function.[8]

Norepinephrine is a monoamine that is synthesized in the central nervous system and sympathetic nerves. The locus coeruleus of the brain plays a vital role in the signaling of norepinephrine. The release of norepinephrine in the brain exerts effects on a variety of processes, including stress, sleep, attention, focus, and inflammation. It also plays a role in modulating the responses of the autonomic nervous system. [8]

Histamine is another neurotransmitter that mediates homeostatic functions in the body, promotes wakefulness, modulates feeding behavior, and controls motivational behavior [8].

Mechanism :

Neurotransmission occurs via the vesicular release of neurotransmitters at presynaptic nerve terminals. Specifically, calcium-evoked exocytosis of the presynaptic vesicles is what enables the release of neurotransmitters into the synapse. Active zones, specialized areas on the presynaptic plasma membranes, tether the neurotransmitter-containing vesicles to the plasma membrane. Once an action potential triggers calcium influx into the presynaptic cleft, active zones undergo fusion with the vesicles, allowing neurotransmitter release. [1]

There are multiple proteins involved in the fusion of neurotransmitter-containing vesicles and the active zone. The soluble N-ethyl maleimide sensitive factor attachment protein receptors (SNAREs) syntaxin-1, SNAP-25, and synaptobrevin-2 together form a SNARE complex, a key component in membrane fusion and ultimately exocytosis. A number of the proteins involved in this process may act as inhibitors and activators of the exocytosis of neurotransmitters from the presynapse. [9]

Pathophysiology :

The neurotransmitter glutamate has been implicated in multiple neurodegenerative studies. Researchers agree that glutamate excitotoxicity undoubtedly has a role in the pathogenesis of Alzheimer's disease, the most common neurodegenerative pathology

affecting the elderly population. Research suggests glutamate excitotoxicity accelerates the progression of Alzheimer's disease. [10]

Glutamate is also implicated in the pathogenesis of Parkinson's disease. Mutations in genes encoding the parkin and DJ1 proteins are present in Parkinson's disease, which are involved in the regulation of excitatory glutamate synapses. These proteins may also protect neurons against glutamate excitotoxicity .[10]

Clinical Significance :

Gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system, is targeted in the treatment of anxiety disorders, insomnia, epilepsy, and other conditions. In particular, these drugs alter GABAergic function by targeting the GABA-A and GABA-B receptors. [11]

Not only does dopamine play an important role in multiple physiological processes, but it also has a role in the pathology of psychiatric and neurodegenerative diseases. Disturbances in the neurotransmission of dopamine are implicated in schizophrenia, psychosis, depression, Tourette syndrome, and attention-deficit hyperactivity disorder. Regarding neurodegenerative diseases, dopamine is related to Parkinson's disease, multiple sclerosis, and Huntington's disease. There has been ample research on the role of dopaminergic neurons in Parkinson's disease. Currently, research suggests that the degeneration of dopaminergic neurons in the substantia nigra pars compacta is involved in the pathogenesis of Parkinson's disease. [11]

Serotonin, a neurotransmitter that controls several neuropsychiatric processes, has been implicated in the pathogenesis of depression. Research has shown that patients with endogenous depression have low plasma levels of tryptophan, a precursor of serotonin. Furthermore, postmortem studies found an association between decreased serotonin levels in the brain and suicide among depressed patients. In light of this, quite a few drugs have been developed that target serotonin in the treatment of depression. For example, tricyclic antidepressants work by increasing serotonin levels in the synapse. [11]

Norepinephrine is involved in the pathogenesis of neuropsychiatric disorders. Changes in locus coeruleus firing, dysregulation of norepinephrine function, synaptic receptor regulation, and norepinephrine availability are what result in pathogenesis. Conditions related to norepinephrine dysfunction include anxiety disorders, mood disorders, attention-deficit hyperactivity disorder, Alzheimer’s disease, and posttraumatic stress disorder. Furthermore, many symptoms in these disorders are directly attributable to norepinephrine dysfunction in the neural circuitry. [11]

A prominent contributor to the pathogenesis of IgE-mediated diseases is the neurotransmitter histamine. Produced in mast cells, histamine exerts its effects in the body by binding to certain histamine receptors. Two of the cardinal features of asthma, bronchospasm and mucosal edema, are directly related to histamine receptor stimulation. [12]

Histamine is also implicated in the pathogenesis of multiple sclerosis, which is characterized by inflammatory demyelination in the central nervous system. In animal models, histamine has been shown to change the blood-brain barrier permeability. This change in permeability led to an increase in cells infiltrating the central nervous system, subsequently increasing neuroinflammation. [12]

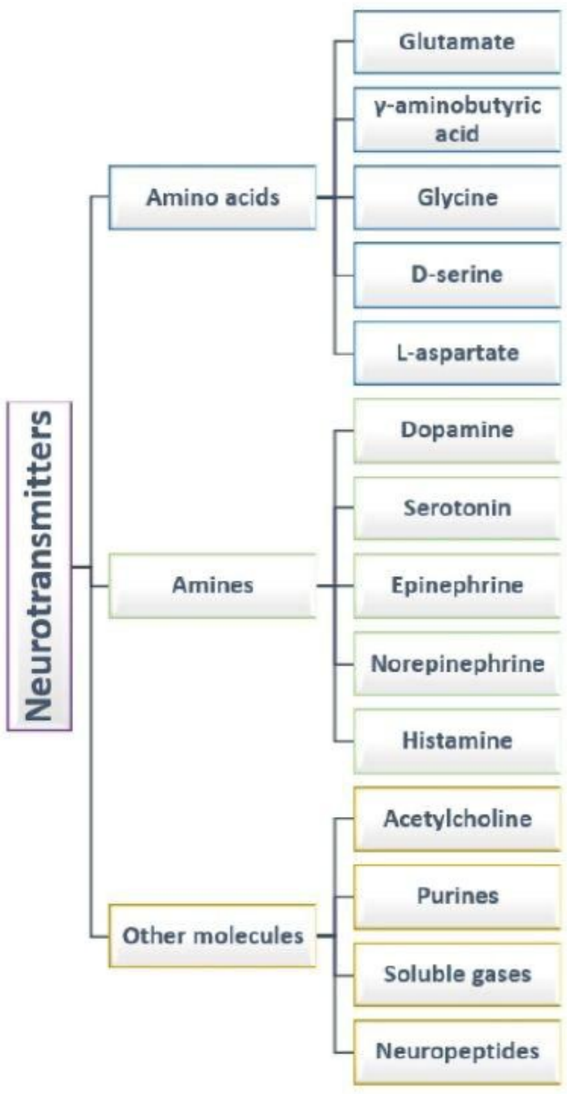

Fig. 3 Classification of neurotransmitters. (Teleanu et al., 2022)

Type of neurotransmitters :

• Amino acid : Amongst NTs, amino acids represent a very important class of chemical messengers, having significant roles in the CNS. [14]

The α-amino acids, such as glutamate and glycine, and γ-amino acids, such as γ-aminobutyric acid (GABA), are involved in fundamental brain processes and the pathogenesis of several disorders (e.g., epilepsy, stroke, dementia) affecting normal brain functioning. [14]

Glutamate is a predominant excitatory NT in the CNS, which can be produced from glutamine and represents the precursor of GABA. [14]

Glutamate is liberated from presynaptic neurons into the synaptic cleft, which leads to the activation of N-methyl-d-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors that further mediate calcium and sodium influxes in postsynaptic neurons. An excess of glutamate may produce excessive Ca2+ influx in the postsynaptic neuron. This further leads to extreme neuronal firing and excitotoxicity, being potentially involved in neurologic conditions, such as multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), and Parkinson's disease (PD). [15]

An essential role in maintaining proper extracellular levels of glutamate through release and uptake mechanisms is played by astrocytes. These cells mediate glutamate uptake and convert a part of it to glutamine, further transporting it to the presynaptic neurons, while certain amounts of the glutamate are released into the extracellular regions via different pathways. These processes regulate the glutamate homeostasis at the tripartite glutamatergic synapse. [15]

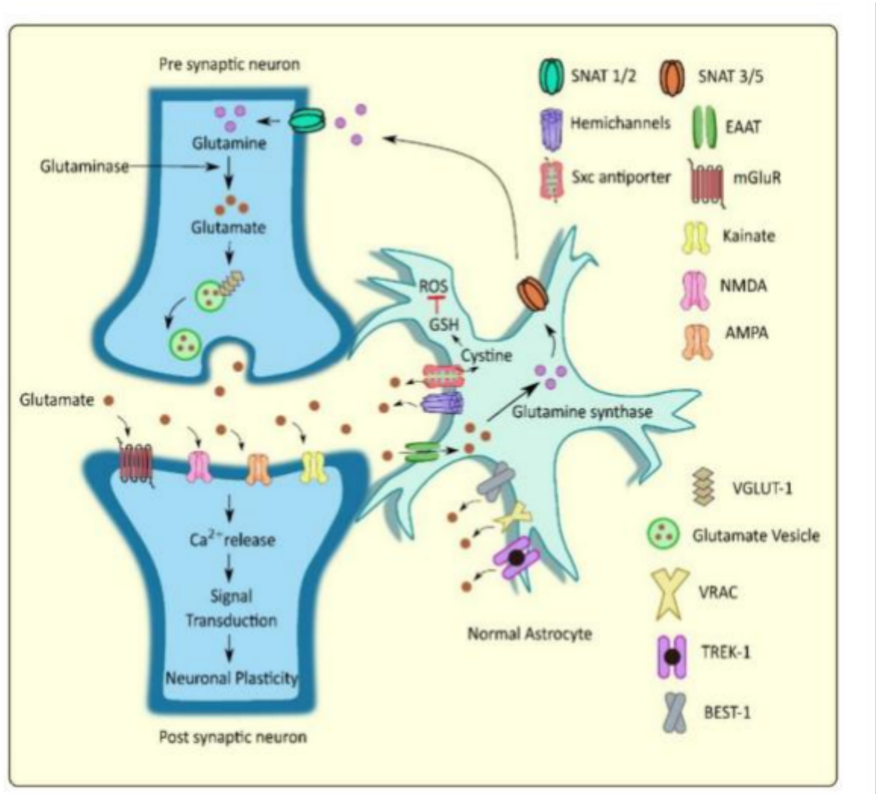

Fig. 4 Schematic representation of glutamate homeostasis at the tripartite glutaminergic synapse. Reprinted from an open-access source. (Satarker *et al*., 2022)

Glutamatergic neurotransmission is highly important in long-term potentiation, contributing to cognitive functions, such as learning and memory formation. [14]

Moreover, it is also responsible for many motor, sensory, and autonomic activities. [17]

Thus, it is crucial to maintain extracellular glutamate levels within a physiological range in order to ensure adequate neuronal transmission and viability. Being involved in such a wide range of functions, an imbalance of glutamate homeostasis can lead to significant neuropathological consequences. [17]

Particularly, its disequilibrium has been linked to several neurological or neurodegenerative disorders, including ALS , MS, Alzheimer's disease (AD),PD,Huntington's disease (HD),and epilepsy [17].

Another important amino acid NT is GABA, the main inhibitory NT in the brain that is formed through glutamic acid decarboxylase. conversion of glutamate to GABA in interneurons. [18]

or is produced by commensal microorganisms from gut microbiota (e.g., Bifidobacterium dentium , Lactobacillus brevis). [18]

Nonetheless, studies revealed that GABA is initially an excitatory NT, as it induces a depolarization instead of hyperpolarization in various regions of the nervous system (e.g., neocortex, hippocampus, hypothalamus, cerebellum, spinal cord). This is caused by the existence of a higher chloride concentration in neurons during the early development of the human body, which is reflected in an outward instead of an inward chloride flux. In contrast, there is a change of expression of sodium-potassium chloride co-transporters and the potassium chloride co-transporters in adults that modifies GABA action from excitatory to inhibitory [18]

Thus, it is widely accepted that low levels of GABA are responsible for the hyperexcitability of neurons [18]

This amino acid exerts its inhibitory activity by two types of specific receptors called GABAA (ionotropic) and GABAB (metabotropic) [18]

GABA neurons comprise a smaller fraction of the total neuronal population than glutamate neurons. Nonetheless, maintaining the balance between inhibitory and excitatory transmission is imperative for normal brain functioning [19] Hence, altered GABAergic neurotransmission has been associated with numerous CNS disorders, such as behavioral disorders, pain, and sleep [18], while stress and depression have been reported to disrupt the function of GABA [19] Explicitly, impaired GABA homeostasis has been linked to various neurological disorders (e.g., autism spectrum disorders ,schizophrenia, epilepsy , and neurodegenerative diseases. [19]

In the spinal cord, the major inhibitory NT is glycine. This amino acid also acts as an NT in the brainstem and medulla, being a co-agonist with glutamate for NMDA receptors. Similar to GABA, glycine has an excitatory activity in early development, being employed in neuronal differentiation, proliferation, and connectivity. In adults, glycine has been observed to be involved in voluntary motor control, sensory processing, auditory, cardiovascular, and respiratory functions. [20]. Another amino acid, NT, is D-serine, a molecule released by glial cells whose functional role in a higher organism is relatively new. D-serine is produced from L-serine by serine racemase, especially in the brain regions rich in NMDA-glutamate receptors [20].

One more amino acid to be included in this section is L-aspartate, whose role as an NT in the CNS has been subject to controversy. Discrepancies have been reported concerning the localization of this NT, as some studies proposed it to be an NT in the visual cortex

and cerebellum, while others show that L-aspartate may be an NT and a neuropeptide-like modulator in the hippocampus. Moreover, the synaptic terminations that contain aspartate vesicles are co-localized with neurons containing glutamate and GABA vesicles. Thus, L-aspartate can play a role in both excitatory and inhibitory pathways. [20]

. Amine : Monoamines are a representative group of NTs with clinical significance in motor functions, emotional responses, motivations, and behavioral function .[65,66]

Dopamine (4-(2-aminoethyl)-1,2-benzenediol) is one of the most important NTs in the mammalian nervous system, as it seems to participate directly or indirectly in almost all physiological functions occurring in the CNS, thus being of great clinical relevance for motor functions and motivational behavior. [21]. Dopamine is also involved in maintaining homeostasis and is a precursor for other catecholamines, such as norepinephrine and epinephrine. [45,69]. Another NT involved in regulating numerous physiological processes is serotonin (5-hydroxytryptamine). This amine NT is implicated in modulating sleep and wake states, gastrointestinal secretion and peristalsis, respiration, vasoconstriction, behavior (e.g., feeding behavior, aggressive behavior, and mood/depression), and neurological function [21]. The vast majority of serotonin (~95%) in the body is produced by enterochromaffin cells of the gut with the aid of the tryptophan hydroxylase enzyme. [21].

Epinephrine and norepinephrine are two monoamine molecules with dual roles: NTs and hormones. As NTs, they are involved in the autonomic nervous system (also known as the “fight or flight” system), composed of the sympathetic and parasympathetic systems. Norepinephrine neurons are found in the locus coeruleus, from where they project to various regions of the brain, including the limbic system. [18]. Histamine is a signaling molecule acting as an NT in the CNS, being engaged in various physiological functions. It is synthesized and released by histaminergic neurons from the tuberomammillary nucleus of the hypothalamus, which further project to other regions of the brain (e.g., amygdala, cerebral cortex, substantia nigra, striatum, thalamus) and spinal cord. Studies have also linked the activity of this NT to disorders, such as AD and schizophrenia. [18].

. Other Molecules : In addition to the above-presented substances, other molecules have also been identified as NTs. One of the most studied such molecules is acetylcholine, the first substance to be characterized and identified as a neurotransmitter in the peripheral nervous system. In the peripheral nervous system, it is released by the postganglion neurons in the parasympathetic system, being responsible for muscle contraction in the neuromuscular system. While in the CNS, acetylcholine plays an essential role in consciousness, being associated with attention, learning, memory, sleep, and voluntary movement control. Cholinergic neurons are localized in several brain and brain stem structures, including the striatum, cranial nerves, and vestibular nuclei. [18]. From the cholinergic presynaptic neurons, acetylcholine is transported to synaptic vesicles via vesicular acetylcholine transporters, and, after the depolarization of neurons, it is released into the synaptic cleft. Further, it enables neurotransmission by binding to acetylcholine receptors. [18]. Being a neuromodulatory agent in many areas of the forebrain, acetylcholine impacts numerous cognitive and motor functions through cortical and subcortical transmission in the cortico-striato-thalamocortical circuits [14]. Thus, its imbalances result in neurologic conditions, including AD, PD, HD,

schizophrenia, myasthenia gravis, and other behavioral, learning, attention, memory, and sleep disorders [18].

Among other molecules recognized as NTs, there can be enumerated purines, such as adenosine triphosphate (ATP) [22], soluble gases (known as gasotransmitters), such as carbon monoxide (CO), nitric oxide (NO), and hydrogen sulfide (H2S), and various neuropeptides,including somatostatin,β-endorphins, vasopressin, neurotensin , substance P, and neuropeptide Y [22].

Among soluble gases, NO is one of the most studied NTs, being well-established as a major signaling molecule and regulator of synaptic plasticity. Moreover, NO was observed to influence D-serine biosynthesis. In more detail, serine racemase is physiologically nitrosylated, inhibiting enzymatic activity and lowering the conversion rate of L-serine to D-serine. NO is produced in response to NMDA transmission and may diffuse to cells generating D-serine as a way of feedback inhibition [23].

Neuropeptide Y is one of the most widely expressed NTs in the nervous system, being the most abundant peptide present in the mammalian brain. This neurochemical was noticed to be employed in various biological processes, including cortical excitability, stress response, food intake, circadian rhythms, and cardiovascular function. Thus, its abnormal regulation raises concerns about developing a broad range of conditions, including neurological diseases, such as epilepsy [23].

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النواقل العصبية، الرسائل الكيميائية للدماغ: القواعد والآليات، مراجعة

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الملخص

يحتوي دماغ الإنسان على ما يُقدّر بـ 86 مليار خلية عصبية. تتواصل هذه المليارات من خلايا الدماغ عبر تبادل الرسائل الكيميائية عند المشبك العصبي، وهو الفجوة الصغيرة بين الخلايا، في عملية تُعرف بالنواقل العصبية. هذه الرسائل الكيميائية عبارة عن جزيئات فريدة تُسمى النواقل العصبية.

يوجد العديد من أنواع النواقل العصبية في الدماغ. لكن بينهما بعض القواسم المشتركة؛ فالناقلات العصبية داخلية المنشأ، أي تُنتَج داخل الخلية العصبية نفسها. عند تنشيط الخلية، تُفرَز هذه المواد الكيميائية العصبية في المشبك العصبي من حويصلات متخصصة تتجمع بالقرب من غشاء الخلية تُسمى حويصلات المشبك العصبي. بعد ذلك، تستطيع مستقبلات محددة على الخلايا المجاورة امتصاص الناقلات العصبية، مما قد يزيد أو يُقلل من قوة الإشارة المنتقلة عبر دائرة عصبية معينة.