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Review Article

Markers of Neurotransmitters: A Review

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Abstract

When a neurological stimulus reaches the end of a nerve fiber, neurotransmitters are produced, and by diffusing across the synapse, they cause the impulse to be transferred to another nerve fiber, a muscle fiber, or some other component. CNS comprises neurotransmitter indicators in the form of genes and proteins that are expressed uniquely in various cells. The major neurotransmitter indicators' neurological, developmental, and pathological functions are demonstrated in this article.

Keywords: Neurotransmitters; Schizophrenia; Membrane Transporters; CB Proteins; Neuropeptides; NT Receptors; Matrix Proteins

Abbreviations

5-HT3: Serotonin Receptor 3; AMPAα: Amino-3-Hydroxy-5-Methyl-4-Isoxazole Propionic Acid; CaBP: Calcium-Binding Protein; CB: Calbindin; CR: Calretinin; ENK: Enkephalin; GABA: Gamma-Aminobutyric Acid; GABAAα1: Gamma-Aminobutyric Acid Receptor A, A1 Subunit; MGluR: Metabotropic Glutamate Receptor; MGluR1a: Metabotropic Glutamate Receptor 1, Splice Variant A; NMDA: N-Methyl-D-Aspartate; NPY: Neuropeptide Y; NT: Neurotransmitter; PV: Parvalbumin; RLN: Reelin; SOM: Somatostatin; Sub P rec: Substance P Receptor; vGAT: Vesicular GABA Transporter; vGluT: Vesicular Glutamate Transporters; VIP: Vasoactive Intestinal Polypeptide

Introduction

A neural impulse releases a chemical component called a neurotransmitter at the end of the nerve fiber, which then transfers the impulse to another nerve fiber. Four neurotransmitters fall within the category of biogenic amines [1]. These include adrenaline, norepinephrine, dopamine, and serotonin. According to the action (direct or neuromodulatory), function (excitation - epinephrine, norepinephrine, or inhibition - serotonin, GABA) or, more specifically, the chemical structure of NTs may be used to classify them. Biochemical monoamines include serotonin, histamine, and catecholamines (dopamine, norepinephrine, and epinephrine). Non-monoamine Examples of NTs (such as ATP and adenosine), purines, and gasotransmitters include nitric oxide, carbon monoxide, and hydrogen sulfide [2].

Neurotransmitter types in the brain

Small, differently expressed proteins known as vesicular neurotransmitter transporters control the entry of certain neurotransmitters (NTs) into vesicles, controlling the number of neurotransmitters released per vesicle before an electrical action potential arrives at a synaptic site. Nine vesicular transporters have been classified into three subgroups based on their substrate selectivity and amino acid sequence similarity. The three vesicular glutamate transporters (vGluT1, vGluT2, and vGluT3), the vesicular excitatory amino acid transporter (VEAT), and the vesicular nucleotide transporter are all members of the SLC17 gene family (VNUT). Vesicular acetylcholine transporter (VAChT) and vesicular monoamine transporters (VMAT1 and VMAT2), which transport serotonin, dopamine, noradrenaline, and histamine, are members of

the SLC18 gene family. Last but not least, the vesicular GABA transporter known as VGAT is a member of the SLC32 gene family [3].

The following action potential depolarizes the presynaptic cell membrane, which causes calcium channels to open and allow Ca2+ to flow into the axonal terminals. Now, calcium-binding proteins (CaBP), including calbindin (CB), calretinin (CR), and parvalbumin (PV), all helpful indicators that are described in more detail below, bind to the ions, controlling intracellular calcium levels. The NT-containing compartments merge with the synaptic membrane when calcium levels are high enough to do so, releasing their contents through exocytosis into the synaptic cleft. Then, neurotransmitters try to bind particular receptors, which are themselves expressed differently on post-synaptic cells [4].

Important neurochemical markers

Membrane transporters

vGluT3

Glutamate is transported and packed into vesicles; it may release alongside GABA or serotonin. Cytoplasmic glutamate buffer. mRNA is expressed in the kidney and liver. Released momentarily in certain cells; Associated with non-syndromic hearing loss [5].

Calcium-binding proteins

CB

Contacts and co-localizes with the plasma membrane Ca2+ pump. Binds calcium ions to control and buffer the amounts in the cytosol. Controls the length of an action's potential. An agent that protects the brain during times of excessive activity. Transcellular Ca2+ migration in intestinal absorptive cells and distal tubules of the kidney. Controls the pancreatic islet cells' ability to secrete insulin. Modulates apoptosis in osteoblasts, which mineralize bone, allegedly via binding to and changing the activity of caspase-3 6]. Controls Ca2+ pools, which are essential for synaptic plasticity. Alzheimer's disease is aggravated by decreased CB expression. Apoptosis in Huntington's disease may be facilitated by a decrease in CB+ neurons. The substantia nigra may degenerate as a result of the loss of CB+ neurons [7].

CR

Expressed in somatosensory pathways and the retina (e.g., cochlear nuclei and olfactory bulb). LTP is also induced. The mesothelium of the lung expresses. Detected in the testicular Leydig cells, ovarian theca lutein cells, and ovarian theca interna cells. In the sustentacular and cortical cells of the adrenal gland, there is weak to moderate expression. Expressed in cutaneous mast cell lesions and mast cell tumors [8]. Hirschsprung disease results in the absence of CR from intestinal nerves. CR was expressed differently in malignant and benign lung tumors in mesothelioma. CR expression in the hippocampus is downregulated in temporal lobe epilepsy [9].

PV

This protein, which is involved in muscle relaxation following contraction, transfers Ca2+ from the cytosol to intracellular storage to hasten fast-twitch fiber relaxation [10]. Interneurons from people with schizophrenia have decreased PV expression [11]. Additionally, in Creutzfeldt-Jakob disease, PV-expressing neurons are particularly susceptible [12].

Neuropeptides

As a result of post-translational changes, pro-peptides, the building blocks of proteins, are broken into peptides. The peptide and the precursor both have the potential to act as molecular markers. Each of these peptides is hydrophilic.

CCK

The actions of glutamate, GABA, dopamine, and serotonin are modified [13]. When exposed to stress, CCK activity increased, indicating that it could be involved in the stress response [14,15]. Memory role [16]. Causes the release of pancreatic enzymes into the intestines and gall bladder contraction. Appetite-suppressant. CCK can be found in the digestive system by day 15 and the neurological system as early as day 8 of embryonic development. Parkinson's illness causes visual hallucinations [17] and colorectal carcinomas create CCK [18].

ENK

Pain perception and analgesia. Stress response. Presence in digestive system peripheral nerves, but uncertain function. Immune cells are found in inflamed subcutaneous tissue. Contributes to cell proliferation. Plays a role in addiction and reward systems. Has been shown to cause seizures [6].

NPY

Control over food intake and fat accumulation. Vasoconstriction in heart tissue is connected to its presence in the peripheral system. Levels of maternal food supply throughout development

are correlated with NPY expression [19]. Obesity, anorexia, and bulimia are all associated with increases in NPY mRNA and NPY release. Connects to alcoholism.

SOM

Shaping of neuronal activity and plasticity during memory formation. Sense of pain. Suppresses the release of prolactin, thyroid-stimulating hormone, and growth hormone. Decreases gastric acid production and discharge in the stomach. Influences cerebellar neuroblast growth, synaptogenesis, and axonal pathfinding [20,21]. Connected to epilepsy. Changes reported in multiple sclerosis, Parkinson's disease, and other neurodegenerative illnesses.

VIP

Utilization and local energy metabolism by glycogenolysis. Neuroprotection. Suprachiasmatic nuclei time is synchronized with the ambient light-dark cycle through circadian rhythm control [20]. Expressed in peripheral nerves, including reproductive, cardiovascular, and respiratory systems (pulmonary vasodilation, increased myocardial contractility, diuresis, increased excretion of Na+ into the urine) (increased blood flow to reproductive organs [21]). In the digestive tract, smooth muscles are relaxed to promote motility; absorption is inhibited, and water and electrolyte secretion are stimulated. The creation of the neural tube [22]. Function in neurogenesis is associated with neurodevelopmental problems, such as fetal alcohol syndrome, autism, and Down syndrome [23]. Temporal lobe epilepsy is linked [24,25].

NT Receptors

MGluR1a

Establishes a variety of chemical and electrical signaling pathways by binding glutamate. Regulates the excitability of cells and ion channels [44]. Auto-regulates synaptic transmission by lowering glutamate release at the pre-synaptic site [45]. LTP and LTD are affected. Peripheral nerves are found in the conducting system, ganglion cells, and atrial nerve terminals of the rat heart. Harm the atrial cells in the heart. Shown in the thymus [46-48]. Reported to be present in osteocytes and to contribute to bone resorption. Expressed in the adrenal gland; may be involved in the stress reaction. Engaged in the experience of pain and expressed in the inner ear. Little part in the development of the embryo and the fetus. Connected to multiple sclerosis [49] and the condition Huntington's [50], implicated in the development of ulcers and melanoma [51].

GABA Aα1

Binds GABA and triggers an electrical post-synaptic inhibitory response. Hippocampus [52, 53] CA1 basket cells and post-synaptic pyramidal cells use synapses differently. PV+ basket cells use this; CCK+ does not [54]. Found in the gonads, the small intestine, and the adrenal gland with little impact on prenatal and embryonic development [55,56]. Links to several neurological and mental health conditions, such as schizophrenia, alcoholism, anxiety disorders, and Huntington's disease [57].

5-HT3

Binds serotonin, a neurotransmitter. Mediates rapid excitatory transmission in the ferret visual cortex, amygdala, and hippocampus as well as rat neocortical interneurons. Receptor antagonists induce LTP in the hippocampus (CA1) and enhance recall and spatial memory. Dopamine release is influenced by agonist and antagonist action. Peripheral nerve system mediation of gastrointestinal pain, bloating, and nausea signals. Because serotonin is present, [58] the impacts of medications that are overused, such as cocaine, amphetamines, nicotine, as well as morphine, are changed.

CB1

Binds natural, synthetic, and endo-cannabinoids. NT release is inhibited pre-synaptically. Mediates short-term GABAergic plasticity, which is characterized by depolarization-induced reduction of inhibition. White blood cells and the spleen; mediates cannabinoid-induced immunosuppression. Heart and gonad expression was also found. [59]. a significant part in drug misuse. Parkinson's illness and schizophrenia are both associated with increased binding.

Sub P rec

Substance P binds. Modifies the inflammatory response, the adaptive stress response, and the perception of pain [26-28]. Vasodilation, modulation of gastrointestinal muscle action [29], and mediation of inflammatory processes. The length of the stress response is shortened by substance P binding to receptors. Before birth, substance P expression is highly elevated; by P14, adult levels are reached. Connected to ongoing pain in the emergence of obesity [30].

Matrix proteins

RLN

Located in the cytosol, dendrite, and extracellular matrix. Enhances the induction and maintenance of LTP, participate in adult neurogenesis, and affects synaptic plasticity. Controls the continued migration of neuroblasts produced in subventricular and subgranular zones and stimulates the formation of dendrites and dendritic spines. Involved in the small intestine's cells' migration and development. Related to the emergence of bone and teeth [31,32]. The liver, blood (plasma and cells), and reproductive organs are other sites of expression. Controls the movement and placement of neurons. Contributes to the stacking of neurons in the cerebellum, hippocampus, and cortex. Various malignancies and Reelin gene dysregulation are connected. Bipolar illness [33] and schizophrenia have been linked to decreased expression. Alzheimer's disease and autism are both related to this [34].

Protein markers of schizophrenia

Schizophrenia is a severe life-changing disease with complicated biological alterations and elevated striatal dopamine [35]. The biggest dopaminergic input to the brain is provided by the substantia nigra (SN), which also gets input from glutamatergic and GABAergic neurons and projects to the striatum, the main target of antipsychotic drugs.

Schizophrenia subjects had elevated TH levels. Tyrosine hydroxylase (TH) and glutamate decarboxylase (GAD67) protein levels were greater in the combined schizophrenia group. The levels of the vesicular glutamate transporter vGLUT2 were comparable in medicated and unmedicated schizophrenia participants, but greater in unmedicated schizophrenic subjects than controls. Treatment-resistant patients exhibited TH and GAD67 levels that were significantly greater than controls. These findings point to increased GABA and dopamine transmission in the SN in schizophrenia, which may be related to responsiveness to therapy [36].

In comparison to controls, SZ-On participants had TH protein and GAD67 levels that were noticeably greater. (In contrast, vGLUT2 levels were considerably higher in the SZ-Off group compared to normal, but vGLUT1 levels in the typical and atypical treatment groups did not vary.) But showing a noticeable rise in the protein levels of TH and GAD67 [37-51].

As evidenced by greater TH and GAD67 levels, schizophrenia is revealed to have enhanced SN dopamine and GABA production when compared to NCs. In terms of treatment status and responsiveness, preliminary data show comparable increases in DA and GABA production in SZ-On and TR individuals. Elevated vGLUT2 levels in the early study of treatment status in SZ-Off participants point to subcortical glutamate dysregulation. Patients using medication had higher levels of the proteins TH and GAD, whereas those not taking medication had higher levels of vGLUT2 [38-51].

Conclusion

According to all evidence and based on confirmed findings, it is clear that the markers of neurotransmitters play a variety of biological roles in addition to their neurological and pathogenic effects on the human body.

Additionally, the presence of neurotransmitter markers can be employed as a diagnostic tool for a variety of illnesses, not just neurodegenerative ones.

As an example, while thinking about schizophrenia, research indicates irregularity in the dopamine and GABAergic systems in the SN, with probable changes in the glutamatergic system. These findings draw attention to possible dopaminergic, GABAergic, and glutamatergic interaction problems. Additionally, we can estimate the impact of antipsychotics used to treat schizophrenia based on the level of certain indicators.

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