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Review Article

Markers of Synaptic Transmission: A Review

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Abstract

Information is passed between neurons and stored for memory formation at synapses, which are the sites for brain communication. Reduced amounts of pre- and postsynaptic proteins cause synaptic degeneration, which is a widespread and early pathogenic event in neurodegenerative illnesses. Other neurodegenerative and neurodevelopmental illnesses, including Alzheimer's disease, reveal disrupted synaptic homeostasis as a pathogenic event, and are hence referred to as synaptopathies. Synaptic biomarkers for certain disorders would aid in deciphering the precise processes of synapse malfunction in various diseases, as well as the pathogenic impact of synaptic degeneration. We shall describe the primary pre- and postsynaptic indicators that are used to diagnose various neurological illnesses in this article.

Keywords: Synaptic Transmission; Pre-Synaptic Markers; Post-Synaptic Markers; Synaptic Vesicle Markers

Introduction

The biological mechanism through which a neuron communicates with a target cell across a synapse is known as synaptic transmission. Chemical synaptic transmission occurs when a neurotransmitter is released from a pre-synaptic neuron and binds to certain post-synaptic receptors. Electrical signals are transmitted across gap junctions in electrical synapse transmission [1]. The following stages are required for chemical synaptic transmission: In the presynaptic nerve terminal, the neurotransmitter is synthesized. The neurotransmitter is stored in secretory vesicles. Neurotransmitter release in the synaptic gap between pre- and post-synaptic neurons is regulated. The presence of specialized neurotransmitter receptors on the postsynaptic membrane, which allows the neurotransmitter to imitate the effects of nerve stimulation when applied to the synapse. A method of stopping the action of a neurotransmitter that has been released [2].

Traditional neurotransmitters, including as acetylcholine (ACh) and norepinephrine (NE), are low-molecular-weight molecules that serve only as neurotransmitters. Glutamate, the brain's primary excitatory neurotransmitter, and glycine, the spinal cord's inhibitory neurotransmitter, are both common and necessary amino acids. Because the membranes of secretory vesicles in glutamatergic and glycinergic nerve terminals have particular transport systems that concentrate and store these amino acids, they can be released via exocytosis in a highly regulated manner, they can serve as neu-

rotransmitters. ACh and GABA, the most common inhibitory amino acid in the brain, are also transported into synaptic vesicles by specialized transport proteins. Synaptic vesicles have an acidic interior with a pH of 5.5, which is maintained by a proton-translocating ATPase of the vacuolar type. The transporters link the absorption of low-molecular-weight neurotransmitters to the electrochemical H+ gradient [3].

At the very beginning of the depolarization of the axon opens voltage sensitive Ca2+ channels in the presynaptic nerve terminal. The influx of Ca2+ results high Ca2+ concentrations at active zones on the plasma membrane which trigger the exocytosis of small synaptic vesicles that store neurotransmitter (NT) that involved in fast neurotransmission. Released neurotransmitter interacts with receptors in the postsynaptic membrane, which couple directly with ion channels and with receptors that act through second messengers, such as G-protein coupled receptors. Neurotransmitter receptors, also in the presynaptic nerve terminal membrane, either inhibit or enhance exocytosis upon subsequent depolarization. Released neurotransmitter is inactivated by reuptake into the nerve terminal by a transport protein coupled to the Na+ gradient, for example, dopamine, norepinephrine, glutamate and GABA; by degradation (acetylcholine, peptides); or by uptake and metabolism by glial cells (glutamate). Clathrin-mediated endocytosis recycles the membrane of synaptic vesicles. Neuropeptides and proteins are stored in larger, dense core granules within the nerve terminal that are released from sites distinct from active zones after repetitive stimulation [2].

Presynaptic markers

The presynaptic terminal, releases neurotransmitters into the synaptic cleft to send a signal to the postsynaptic neuron. The action potential is transferred through the presynaptic neuron and down the axon towards the presynaptic terminal when the membrane at the dendrite depolarizes. Calcium enters the cell via ion channels when the axon terminal depolarizes. Presynaptic terminals have a lot of docked vesicles with neurotransmitters in them. The synaptic active zone is the name given to this region. Due to the high amounts of calcium in the cell after depolarization, these docked vesicles fuse their membranes with the cell membrane and release the stored neurotransmitters into the synaptic cleft. The discharged neurotransmitters attach to post-synaptic neuron receptors, thereby transmitting the signal to the postsynaptic cell [1].

Piccolo, bassoon, CASK, SNAREs, SNAP25, VAMP, and syntaxin are all proteins found in the synaptic active zone. Presynaptic markers specific to those distinct proteins are used in immunostaining of the synaptic active zone. We are committed to creating cutting-edge presynaptic markers, like as monoclonal antibodies, polyclonal antibodies, and antibody conjugates, to help in the study of signal transduction in neuroscience [4].

Postsynaptic markers

The postsynaptic membrane receives signals from the presynaptic terminal within the neural synapse. The signals are received by membrane-bound receptors that bind to neurotransmitters in the synaptic cleft. When a neurotransmitter binds to an ionotropic receptor, an ion channel opens, enabling ions to flow into or out of the cell. Ion flow affects the postsynaptic membrane potential. A signaling pathway is triggered when a neurotransmitter interacts to a metabotropic receptor via the utilization of second messengers. The postsynaptic membrane is home to a thick cluster of hundreds of specialized proteins known as the postsynaptic density (PSD). Postsynaptic density-95 (PSD95), neuroligin, SAP102, SAPAP, SHANK, and calcium/calmodulin-dependent protein kinase II have all been found in the PSD. Neuroscientists may ask and answer difficult research questions regarding how signals are transmitted and received inside the brain by immunostaining the PSD via known protein targets. We are committed to creating cutting-edge postsynaptic markers to help in neuroscience research, including as monoclonal antibodies, polyclonal antibodies, and antibody conjugates [5].

Pre- and postsynaptic biomarkers

Biomarkers for synaptic dysfunction are classified as pre- or postsynaptic based on the protein's location. There are now four major presynaptic biomarkers: growth-associated protein 43 (GAP-43), synaptosomal-associated protein 25 (SNAP-25), synaptotagmin-1, and α -syn, and one postsynaptic biomarker, neurogranin.

GAP-43

GAP-43 is a presynaptic protein that is involved in memory and information storage. It is anchored on the cytoplasmic side of the presynaptic plasma membrane and is mostly expressed in the adult brain's hippocampus, entorhinal cortex, and neocortex. GAP-43 CSF levels were shown to be considerably higher in patients

with AD compared to controls as well as in patients with other neurodegenerative illnesses. CSF GAP-43 levels were likewise higher in preclinical and clinical Alzheimer's disease patients compared to controls. Changes in CSF GAP-43 levels have also been recorded in progressive multiple sclerosis (MS), inflammation, stroke, and Parkinson's disease (PD) [6].

SNAP-25

Because it is required for vesicular exocytosis, neurite outgrowth, and LTP, SNAP-25 plays an important role in neuronal survival and cognitive function. SNAP-25, in collaboration with VAMPs and syntaxins, generates SNARE complexes that mediate synaptic vesicle apposition to the presynaptic membrane, allowing for Ca2+-triggered vesicle fusion during exocytosis [7]. Even in the early stages of Alzheimer's disease, SNAP-25 has been demonstrated to have considerably increased CSF levels. SNAP-25 levels in the CSF have also been reported to be elevated in individuals with Parkinson's disease and sporadic CJD. SNAP-25 has been linked to a number of mental disorders, including attention deficit hyperactivity disorder (ADHD), schizophrenia, and bipolar disorder [7]. SNAP-25 has two splicing variants: SNAP-25A and SNAP-25B. However, Barakauskas., *et al*. [8] discovered considerably lower levels of overall SNAP-25 and SNAP-25A in postmortem brain tissue, demonstrating a particular differential expression of SNAP-25A in schizophrenia.

Synaptotagmin-1

Synaptotagmin-1 is a calcium sensor vesicle protein that is required for hippocampus neurons to release neurotransmitters quickly. It is a transmembrane protein with two Ca2+-binding domains that is anchored in vesicle membranes. Synaptotagmin-1 cause's vesicle fusion in response to Ca2+ binding at high concentrations, however the specific molecular pathways are unknown. Synaptotagmin-1 levels were lower in a CSF pool from individuals with early-onset Alzheimer's disease. Found a substantial rise in synaptotagmin-1 in individuals with AD and MCI, with MCI owing to AD having the highest level. In addition to synaptotagmin-1, the concentrations of GAP-43 and SNAP-25 were considerably higher in AD and MCI-AD compared to the other diseases.

Alpha-synuclein and its forms

The synuclein family includes the soluble proteins α-, β-, and γ-synuclein, which are encoded by three distinct genes. α -syn is the most researched of them [9].

Total α-syn

Several investigations have indicated that people with Parkinson's disease had considerably reduced levels of t -α-syn (10%-15%). Other synucleinopathies, including as DLB and MSA, have demonstrated a comparable reduction. T -α-syn levels appear to be higher in Alzheimer's disease. CJD patients had a more dramatic rise in CSF t -α-syn [10]. The gradual decline in synapse number may result in a drop in α-syn synthesis. α-syn is mostly expressed outside of the CNS and is plentiful in blood, with red blood cells (RBCs) being the primary source. Many researches are being conducted to evaluate α-syn as a blood biomarker for dementias. According to a meta-analysis, plasma t- α-syn is considerably greater in Parkinson's disease [11]. Reduced serum concentrations of t-α-syn in DLB were discovered in research by Laske., *et al.* [12]. A few investigations on RBC t-syn have also revealed considerably lower amounts of the protein in PD and AD.

Phosphorylated, oligomeric, and aggregated forms of α-synuclein

In Parkinson's disease, oligomeric α-syn in CSF appears to be enhanced. Parnetti., *et al*. [13] discovered that utilizing the ratio of oligomeric/total α -syn in CSF can increase the diagnosis accuracy of Parkinson's disease. Significantly increased levels of PD have been documented in plasma, serum, and RBC. Increased o-α-syn saliva levels were detected in PD patients in research by Vivacqua., *et al.* [14]. Phosphorylated α-syn, one of the key illness-associated posttranslational modifications (PTMs), has been discovered to be higher in Parkinson's disease [15], and its diagnostic accuracy enhances when its ratio to other α-syn forms is used [16]. Phosphorylated- α-syn has also been linked to an increase in CJD. Plasma p-α-syn has been reported to be considerably elevated in Parkinson's disease [17].

Neurogranin

Neurogranin is an intracellular protein found in the dendritic and postsynaptic compartments of neurons' synaptic spines [18]. It binds to the Ca2+-signaling mediator calmodulin via its central IQ domain [19], increasing signaling for processes involved in memory formation, and to phosphatidic acid at the inner plasma membrane [20]. CSF neurogranin was shown to be elevated in AD in a first investigation using immunoprecipitation and Western blot [21]. This rise appears to be unique to Alzheimer's disease. Aside from full-length neurogranin, CSF primarily includes C-

terminal half fragments [22]. Two intracellular enzymes that can cause cleavages at the functionally crucial IQ domain and at the very C-terminus have been discovered [22]. Overall, neurogranin appears to be a helpful biomarker in CSF for detecting early neurodegeneration, and it appears to be reasonably specific for AD among different tauopathies.

Emerging synaptic biomarkers

Neuronal pentraxins

NPTX1/NP1) and II (NPTX2/NP2), as well as the neuronal pentraxins receptor (NPTXR), are abundantly expressed at excitatory synapses, where they bind to AMPA receptors and are thought to play a role in synaptic plasticity [23]. In the AD and MCI groups, all three neuronal pentraxins had lower CSF levels [24]. Pentraxins levels in the CSF are also linked to cognitive function and hippocampus volume [25]. Furthermore, both NPTXR and NPTX1 were reported to be diminished in atypical parkinsonian diseases in research by Magdalinou., *et al.* [26] (PSP, MSA, CBD)

SV2A

SV2A is a transmembrane protein found in synaptic vesicles that is extensively expressed in brain neurons. SV2A is found in dense-core and tiny synaptic vesicles [27]. It plays a role in neurotransmitter release control [28] as well as synaptotagmin expression and trafficking [29]. In Alzheimer's disease, there is a hypo metabolism of SV2A. The reduction in hippocampal binding is consistent with the early loss of entorhinal cortical cell projections to the hippocampus and hippocampal SV2A reductions found in postmortem AD brain tissue investigations [30]. Changes in [11] UCB-J PET have recently been seen in Parkinson's disease, cortical basal syndrome, and epilepsy, indicating that SV2A might be a universal marker for synaptic density. SV2A has recently been discovered in CSF and confirmed as a virus. SV2A has recently been discovered in CSF and demonstrated to be decreased in Alzheimer's disease [31].

Miscellaneous: other emerging synaptic biomarkers

Rab proteins are important synaptic proteins involved in both neurotransmitter receptor recycling and neurotransmitter exocytosis. Ras-related protein 3a (Rab3a), which regulates Aβ synthesis and interacts with α-syn [32], is very prevalent in brain tissues and has been linked to various neurodegenerative illnesses (AD, PD, and DLB). The granin family, which consists of dense-core vesicle proteins involved in neuropeptide synthesis and secretion, is a second significant protein family for neurotransmitter exocytosis. The proteins have been linked to not just neurodegenerative illnesses like Alzheimer's, but also synaptopathies like schizophrenia and depression [33]. The CSF concentrations of three major granins, chromogranin-A, secretogranin-2, and neurosecretory protein VGF, were reported to be considerably reduced in AD [34]. Contactin-2, a cell-adhesion protein that interacts with APP and beta-secretase 1, is another synaptic protein involved in the pathophysiology of AD (BACE1). In Alzheimer's disease, Chatterjee., *et al.* observed that the protein was diminished in both brain tissue and CSF. All three synuclein protein family members α, β, γ were measured in CSF for the first time by Oeckl., *et al*. [35]. All synuclein concentrations were shown to be higher in Alzheimer's disease and Parkinson's disease, but not in PD, DLB, or atypical parkinsonian syndromes.

14-3-3

The 14-3-3 protein family consists of seven isoforms that are significantly expressed in the brain. They're also abundant in presynaptic synapses and essential modulators of synaptic activities like neurotransmission and plasticity. CJD has been detected using the 14-3-3 protein. 14-3-3 isoforms have been identified to interact with important proteins like as tau and -syn, as well as co-localize in LB in PD and NFTs in AD. They've also been related to neurodegenerative illnesses including Parkinson's, Alzheimer's, and CJD, as well as neuropsychiatric disorders like schizophrenia and bipolar disorder [36]. Antonell., *et al.* discovered considerably higher gamma 14-3-3 concentrations in both FTD and AD in a recent research. In comparison to FTD, elevated concentrations were discovered in a prodromal stage for AD, and the protein level was also considerably higher at later stages.

Synaptophysin

Because it is the most abundant integral synaptic vesicle and plasma membrane protein. Synaptophysin is one of the most often utilized synaptic biomarkers in immunohistochemistry. Synaptophysin content has been found to be decreased in postmortem brain tissue from Alzheimer's disease patients [37]. Due to its high hydrophobic profile, it is sometimes undetectable in CSF [38]. It has, however, lately been discovered in exosome preparations from bodily fluids [39].

Neuronal-derived exosomes

Isolating neuronal exosomes from blood has been used in a recent study to find novel synaptic biomarkers. Blood is a more

easily accessible peripheral fluid than CSF, which requires a more intrusive process to remove. Blood, on the other hand, has the disadvantage of being further removed from the brain, resulting in a peripheral contribution to protein levels. The benefit of studying neuronal exosomes enriched from blood is that it allows researchers to use blood while also reflecting brain pathologic processes. In individuals with AD and FTD, Goetzl., *et al*. [40] showed dramatically reduced neuronal-derived levels of Synaptophysin, synaptopodin, synaptotagmin-2, and neurogranin. GAP-43 and synapsin-1 had considerably decreased levels solely in AD, according to the same study. In a separate investigation by Goetzl., *et al*. [41], plasma neuronal–derived exosome levels of NPTX2, neurexin 2, GRIA4, and neuroligin 1 were shown to be considerably lower in AD, with GluR4 and neuroligin 1 being linked with cognitive decline. α-syn, which has been discovered to have higher amounts in PD [42], is another protein that has been measured in neuronal exosomes.

Conditional synaptic vesicle markers

Information is transferred between neurons primarily by the release of neurotransmitters from synaptic vesicles (SVs) at presynaptic release sites. The placement of SVs inside a neuron can thus provide useful information regarding the location of neurotransmitter release within a neuron as well as the downstream neurons to which a specific neuron is linked, which is crucial for understanding how neural circuits create behavior. Synaptic vesicles (SVs) are the building blocks of chemical synaptic transmission, the most common kind of neural communication in the nervous system. Understanding how a specific neuron communicates information to others and, ultimately, how brain circuits contribute to the creation of behavior, requires the capacity to accurately localize synaptic vesicles inside a neuron. The subcellular location of SVs in a neuron provides insight into where neurotransmitter release may take place, as well as which nearby neurons may or may not be receiving neurotransmitter-based information. In order to comprehend neuronal communication and the mechanisms by which behavior is created, a conditional SV marker that properly represents the distribution of SVs in individual neurons is desirable. Synapse damage and loss are fundamental to the pathophysiology of Alzheimer's disease (AD) and lead to reduced cognitive function [43].

Conclusion

The pathophysiology of synaptopathies and the importance of synapses in cognition offer a compelling case for the necessity for the application of synapse pathology biomarkers as indicators of cognitive and synaptic function. Synaptic biomarkers may be used in clinical settings to relate synaptic degeneration to a patient's cognitive state and deterioration, and they might be used in conjunction with cognitive tests to provide a more exact description of the patient's symptoms, particularly in the early stages. Furthermore, synaptic biomarkers might aid in understanding the underlying pathogenic processes that occur during cognitive illnesses, since various proteins may represent distinct pathways, aiding in diagnosis. Furthermore, synaptic biomarkers can be employed during medication development to track the efficacy of therapies on synapse functioning in clinical trials.

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