American Journal of Alzheimer's Disease & Other Dementias®
25(7) 547-555

DOI: 10.1177/1533317510382893
http://aja.sagepub.com
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Disruption of the Postsynaptic Density in Alzheimer's Disease and Other Neurodegenerative Dementias

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Abstract

The most common causes of neurodegenerative dementia include Alzheimer's disease (AD), dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD). We believe that, in all 3, aggregates of pathogenic proteins are pathological substrates which are associated with a loss of synaptic function/plasticity. The synaptic plasticity relies on the normal integration of glutamate receptors at the postsynaptic density (PSD). The PSD organizes synaptic proteins to mediate the functional and structural plasticity of the excitatory synapse and to maintain synaptic homeostasis. Here, we will discuss the relevant disruption of the protein network at the PSD in these dementias and the accumulation of the pathological changes at the PSD years before clinical symptoms. We suggest that the functional and structural plasticity changes of the PSD may contribute to the loss of molecular homeostasis within the synapse (and contribute to early symptoms) in these dementias.

Keywords

Alzheimer's disease, dementia with Lewy bodies, frontotemporal dementia, postsynaptic density

Introduction

Dementia involves progressive impairment of memory, cognition, language, and behavior. Common neurodegenerative diseases include Alzheimer's disease (AD), dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD). Alzheimer's disease is the most frequent cause of neurodegenerative dementia, accounting for approximately 60% of patients with dementia. Dementia with Lewy bodies is arguably the second most common type of neurodegenerative dementia, which accounts for 10% to 20% of dementia cases. Frontotemporal dementia is another common type of neurodegenerative dementia, dominated by frontal lobe degeneration of the non-AD type.[1] Frontotemporal dementia includes Pick's disease, primary progressive aphasia, and dementia in motor neuron disease.[2,3]

The pathological characterizations of AD, DLB, and FTD are complicated and overlap. β-Amyloid (Aβ) plaques and hyperphosphorylated tau-containing neurofibrillary tangles are the pathological hallmarks of AD. Most of α-synuclein inclusions, called Lewy bodies (LB), are demonstrated in the cortex and subcortical regions in DLB. However, aggregates of α-synuclein are also present in the Lewy body variant of AD. Also, Aβ plaques and hyperphosphorylated tau are frequent in DLB cases. Tau is a microtubule-associated protein stabilizing microtubules as tracks for axonal transport.[4] The pathological hyperphosphorylation of tau is also linked to FTD development. Although these aggregates of misfolded proteins overlap, evidence suggests that dysfunction and loss of the synapse might be a common pathological mechanism underlying the cognitive decline and memory loss in these neurodegenerative diseases.[5-11]

Most excitatory synapses terminate on dendritic spines for memory formation.[12] Spine size is directly related to synaptic strength, and this size is proportional to the area of the postsynaptic density (PSD).[12-14] The PSD is an electron-dense thickening of membrane comprised of a proteinaceous network including glutamate receptors, adhesion molecules, scaffolding proteins, cytoskeletal proteins and associated signaling molecules. It is involved in a number of signaling pathways controlling synaptic plasticity and maintaining synaptic homeostasis. Synapses are continuously formed, eliminated, and remodeled throughout adulthood including synaptic protein synthesis, degradation, and modification. The stabilization of a new synaptic protrusion is associated with an increase in the size of the spine head and correlates with activity-driven PSD proteinaceous network formation. At this proteinaceous network, postsynaptic density protein 95 (PSD-95) is believed to play a role in synapse maturation, as it is one of the earliest detectable proteins in the PSD.[15] PSD-95 induces clustering

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of a number of neurotransmitter receptors and scaffolding proteins.[15,16] PSD-95 is coupled to Shank by guanylate kinase-associated protein (GKAP). Shank proteins directly regulate the formation and morphology changes of spine.[17] The formation of PSD95-GKAP-Shank complex is the earliest event at the formation of the new postsynaptic site.[18] The elimination of synapse is associated with a decrease in the size of the spine head and correlates with activity-driven PSD proteinaceous network degradation.[19]

In AD, preferential loss of postsynaptic compared with presynaptic elements has been suggested based on decreases in drebrin, a postsynaptic actin-binding protein.[20,21] Here, the pathological changes of the postsynaptic region, PSD, are discussed in the brains of patients with AD, DLB, and FTD. The dynamic rearrangement of PSD could be the structural basis for the synaptic plasticity, the assembling and elimination of PSD components might lead to a fast alteration of synaptic structures underlying normal function or pathological changes of synapse.[22-24] It is possible that the destruction of PSD is common mechanism at selective brain regions for these neurodegenerative diseases. Currently, the soluble oligomers of Aβ have been considered the initiator of synaptic dysfunction in AD.[25,26] The pathogenic soluble oligomers of Aβ exist at damaged synapses in AD[27] and associate with PSD in vivo.[28] After PSDs were isolated and were analyzed by proteomics, glutamate receptors, PSD-95, Shank3, and synGap were shown to be dramatically altered in the frontal cortical tissues of patients with AD.[11] The pathological changes of these proteins might directly or indirectly affect the dendritic spine and synapse function and homeostasis.

The proteins at PSD can be subdivided into classes of (1) membrane-bound receptors and channels, (2) scaffolding and adaptor proteins, (3) cytoskeletal proteins, (4) cell-adhesion proteins, (5) modulatory enzymes including kinases/phosphatases, and others.[29-31] Here, we focus to discuss the pathological changes of structure-relevant proteins at PSD in these neurodegenerative dementias.

Synaptic Receptors and Channels

Glutamate Receptors

Glutamate receptors predominantly control synaptic plasticity and memory function. The various subtypes of glutamate receptors, ionotropic glutamate receptors (*N*-methyl D-aspartate [NMDA] and alpha-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid [AMPA]), and metabotropic glutamate receptors (mGluR) are integrated at the PSD in dendritic spines.

N-methyl D-aspartate receptor. The alterations of glutamatergicsynapses have been shown to be one of the earliest events and have long been considered the best pathological correlate of cognitive decline in AD.[32] The evidence accumulated from the cellular to the clinical level demonstrated the glutamate receptors are dysfunctional in the initial stages of AD. In vitro, the oligomers of Aβ suppress NMDA receptor-mediated long-term potentiation (LTP), a synaptic mechanism underlying memory and cognitive processing.[33] Interestingly, the NMDA receptor not only plays a critical role to regulate synaptic function but also has effects on amyloid precursor protein (APP) processing to release Aβ. Sublethal NMDA receptor activation increases the production and secretion of Aβ42.[34] The oligomers of Aβ may reduce NMDAR-dependent Ca influx into the spine head.[33] The decrease of calcium influx through the synaptic NMDA receptors may inhibit nonamyloidogenic alpha-secretase-mediated APP processing and increase the production of Aβ.[35] Therefore, the deregulation of the glutamatergic neurotransmission may change the expression of APP and increase Aβ production at synapse. Deregulation of APP metabolism may exaggerate the dysfunction of glutamatergic receptors in early AD development.

Alpha-amino-3-hydroxy-5-methyl-4- isoxazole-propionic acid receptor. The oligomers of Aβ also disrupt the function of the AMPA receptor and reduce its expression on the synapse by Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII). This kinase is also altered in AD.[36] In vivo, the early reports show a decrease of AMPA binding sites in AD brain.[37] Recently, reports show NMDA receptor and AMPA receptor dramatically reduced at the PSD,[11,38] which suggests the AMPA receptor (at the PSD) could also be an effective target along with the NMDA receptor for AD intervention. Interestingly, the AMPA receptor is also significantly reduced in the FTD brain, indicating that the AMPA receptor could also play an important role in synaptic dysfunction in FTD.[39]

Metabotropic glutamate receptor. mGluRs are G-protein-coupled receptors, which are classified into 3 groups on the basis of signal transduction pathways and their pharmacological profiles. Group I mGluRs comprise mGluR1 and mGluR5. These subtypes are localized at the PSD area. The antagonists of group I mGluRs are neuroprotective. mGluR1 and mGluR5 antagonists also protect neuron in response to the administration of NMDA.[40,41] However, the neurotoxicity of Aβ is exacerbated by application of the mGluR1 antagonist (RS)-1-aminoindan-1,5-dicarboxylic acid (AIDA),[42] which implies the oligomers of Aβ might affect multiple targets. The dysfunction of group I mGluR has been hypothesized to be similar between AD and DLB. [43] Unfortunately, after the synapse was fractionated, the protein level of mGluR1 is not reduced in AD.[11]

Acetylcholine Receptors

In addition to dysfunction of glutamate receptors, the early symptoms of AD and DLB also appear to correlate with dysfunction of cholinergic synapses.[44,45] Acetylcholine receptors are classified as muscarinic acetylcholine receptors (mAChR) and nicotinic acetylcholine receptors (nAChR). Nicotinic acetylcholine receptors are known as ''ionotropic'' acetylcholine receptors. The nAChRs are ligand-gated ion channels. The clustering of α7nAChR at PSD is retained through interactions with PSD components. Acetylcholine receptors can aid in

activating glutamatergic synapses and work together with AMPA receptors to mediate postsynaptic excitation throughout life.[46] In the AD brain, oligomers of Aβ may block the activity of α7nAChR effecting on the endocytosis of NMDA receptors.[47]

Dopamine Receptor

Dopamine is an important neurotransmitter in cognitive function, and the multiple dopamine receptor subtypes contribute to different aspects of learning and memory.[48] The D2R-NR2B interaction effects on the association of CaMKII with NR2B at PSD.[49] In AD, the loss of the D2 receptor-enriched modules contributes to disturbances in information processing in these high-order association cortices and in the hippocampus and may promote the cognitive and noncognitive impairments.[50,51] Striatal D2/D3 receptors are increased in patients with AD having delusions.[52] In DLB, D2 receptors may alter regulation of the striatal projection neurons,[44] and the reduction of D2 receptors are correlated with cognitive decline of DLB.[53]

Serotonin receptor

Serotonin (5-hydroxytryptamine; 5-HT) regulates spine density in the hippocampus in both developing and adult animals.[54] 5-HT2A receptors target spines of pyramidal neurons,[55] and 5-HT2A receptors are colocalized with the NMDA and AMPA receptor subunits: NR1 and GluR2 in the hippocampal dentate gyrus and are colocalized with PSD-95 and with multiple PDZ protein-1 (MUPP1) in PSD.[56] PSD-95 profoundly modulates 5-HT2A and 5-HT2C receptor function.[57] Activation of 5-HT2A/C receptors involves in the functional regulation of NMDA receptors at pyramidal neurons of prefrontal cortex to control cognitive and emotion.[58] The activation of 5-HT2A receptors can induce a transient increase in dendritic spine size and phosphorylation of p21-activated kinase (PAK). p21-Activated kinase show pathological relocation at synapse in AD brain.[55] The protein level of 5-HT2A receptors is also profoundly reduced in patients with AD,[59] in patients with mild cognitive impairment (MCI),[60] and in patients with FTD.[61] The reduction of 5-HT2A receptors may be correlated with the cognitive decline among these diseases.[62]

Insulin Receptor

Insulin receptor is a tyrosine kinase, many of its actions require accessory molecules known as insulin receptor substrates (eg, IRS-1, IRS-2, and IRS-3).[63] Insulin receptor is concentrated at synapses and is a component of the PSD. The insulin signaling plays an important role in synaptic function.[64] The insulin receptor tyrosine kinase substrate p53 (IRSp53) is highly enriched in PSD fraction in brain. Although the soluble oligomers of Aβ caused major downregulation of plasma membrane insulin receptors (IRs), via a mechanism sensitive to CaMKII and casein kinase II (CK2) inhibition,[65] however, the protein level of IRSp53 did not show pathological change at PSD in AD.[11]

Lipoprotein Receptors

Apolipoprotein E (apoE) is a cholesterol transport protein. Apolipoprotein E is a genetic risk factor for late-onset AD.[66,67] Apolipoprotein E receptors have recently been recognized as pivotal components of the neuronal signalling machinery.[68] Apolipoprotein E receptors effect on intraneuronal signaling cascades through NMDA-type glutamate receptors.[69] The effects of apoE receptors on NMDA receptor signaling may be mediated by the interaction between apoE receptors (LRP1 or apoER2) and PSD-95.[70] At the postsynaptic membrane, LRP1 interacts with the PSD-95[71] and might be part of a large postsynaptic density protein complex where LRP1 would modulate the conductance of neuronal ion channels.[72]

The receptors of apoE, very-low-density lipoprotein (VLDL) receptor and apoE receptor 2 (apoER2), are also receptors for reelin. The location of reelin in spines, PSD, and terminals suggests that reelin has a role in synaptic remodeling and in LTP formation.[73] Reelin is upregulated in the brain and cerebrospinal fluid (CSF) in several neurodegenerative diseases.[74] Reelin-mediated signaling may contribute to neuronal dysfunction associated with AD.[75] Reelin interacts with APP, potentially having important effects on neurite development.[76] Interestingly, many of APP-interacting proteins also interact with the family proteins of apoE receptors. Both APP and apoE receptor affect neuronal migration and synapse formation in brain.[77] Apolipoprotein E receptor may play important roles in the dysfunction of the synapse and in β-amyloid formation in AD development.

Neurotrophic Factor Receptor

Neurotrophins regulate the survival and differentiation of afferent neurons. The neurotrophic factors, including BDNF, NGF, bFGF, and IGF1, activate receptors that possess intrinsic tyrosine kinase activity. Among these receptors, trkB, a high-affinity receptor for BDNF, is identified at PSD. The presence of trkB at the PSD is consistent with a role for neurotrophins in the regulation of synaptic activity via direct postsynaptic mechanisms.[78] Synaptic actions of BDNF are ''gated'' by cyclic AMP (cAMP). Cyclic AMP regulates BDNF function in mature hippocampal neurons by modulating the trafficking of TrkB to dendritic spines, possibly by promoting its interaction with PSD-95.[79] In amyloid-transgenic mice, BDNF can reverse synapse loss, and improve cell signaling and restore learning and memory, which implies the BDNF may have potential to reverse neuronal atrophy (and cognitive impairment) in AD.[80,81] The interesting question is whether BDNF normalizes protein synthesis at the spine and repairs the function and structure of the proteinaceous network at the PSD in neurodegenerative dementias.

Synaptic Scaffolding and Adaptor Proteins

Scaffold proteins assemble neurotransmitter receptors, signal transduction components, actin-based cytoskeleton, adhesion

molecules, and modulatory enzymes at PSD. The major scaffolding molecules are membrane-associated guanylate kinase (MAGUK) protein PSD-95 and "master organizing" molecule Shank protein. The pathological changes of these scaffold proteins may be involved in the synaptic dysfunction in neurodegenerative dementias.

Membrane-Associated Guanylate Kinase Proteins

Membrane-associated guanylate kinase proteins belong to a family of synaptic proteins homologous to the product of the *Drosophila* gene Disc Large and include PSD-95, SAP97, chapsyn-110/PSD-93, and SAP102. Modifications of MAGUK proteins in the glutamatergic synapse are common events in several neurodegenerative disorders.[82] PSD-95 is a critical component in the family of MAGUK proteins. PSD-95 organizes ionotropic glutamate receptors and their associated signaling proteins to regulate the strength of synaptic activity. Although the level of PSD-95 protein is sometimes changed in the brains of patients with AD, results have been inconsistent among various laboratories. An increase of PSD-95 protein levels occurs in the brain tissues of learning-impaired rats[83] and human frontal cortex, both at the synapse[84] and in the PSD fraction.[11] However, a decrease of PSD-95 protein levels occurs in the AD temporal cortex,[85] which suggests that the synaptic proteins could show different changes at selective regions in the brains of patients with neurodegenerative disease.

PSD-95 regulates protein trafficking and clustering of cell surface receptors and ion channels.[86] PSD-95 has been shown to influence surface expression of NMDA receptors and to regulate AMPA receptor insertion and retention at the synapse.[87] Mice lacking PSD-95 show normal NMDA receptor clustering and function but reduced AMPA receptor function.[88] The pathological distribution of PSD-95 could alter function of NMDA receptor and AMPA receptor at PSD in AD,[11] which may provide a possible means to alter synaptic strength.

In addition to modulating ion channel clustering and function, PSD-95 interacts with GKAP and may influence the recruitment of Shank, a molecule coupled to the actin-binding protein cortactin and the metabotropic glutamate receptor-interacting protein Homer to control spine morphology. Shank multimers assemble in large, sheet-like structures and may serve as a platform foundation for many PSD structures.[89]

Shank

Shanks are the products of 3 genes, *Shank1*, *Shank2*, and *Shank3*. Shank proteins form the postsynaptic platform in PSD and organize NMDA receptor complex, AMPA receptor complex, and mGlu receptor complex.[29] Shanks play a critical role in integrating the various postsynaptic membrane proteins, cell-adhesion molecules, signal components, other scaffolding proteins, and actin-based cytoskeleton at the PSD protein network. These interactions place Shanks in the heart of the deeper layer of PSD proteins.[15] The dynamic rearrangement of PSD seems to be the structural basis for the synaptic regulation and synaptic plasticity that may be involved in memory formation.[24] In AD brain, oligomers of Aβ attack the postsynaptic region[26] and associate with PSD,[28] leading to inappropriate activity of NMDA-receptor at PSD[90]; NMDA receptor activity is also dependent on integrity of its subunit composition and activation of its downsignal pathway and adjacent non-NMDA glutamate receptors. The total NMDA receptor (NR1) and AMPA receptor (GluR2) are significantly lost at PSD in AD cases.[11] The complex of NR1 and/or GluR2-PSD 95 is linked to Shank proteins. Shanks show dramatic pathological change in AD.[11] Shanks interact with several actin-binding proteins, including α-fodrin/spectrin, cortactin, actin-binding protein 1 (Abp1), and IRSp53.[29] The pathological changes of Shank proteins may directly/indirectly effect on the dynamics of actin in synaptic spine.

Cytoskeletal Proteins

The ability of globular actin (G-actin) to rapidly assemble and disassemble into filaments (F-actin) is critical to many cell behaviors. At the synapse, the dynamics of actin determine spine architecture by the GTPase-activating protein SynGAP, which has recently been shown to regulate both steady-state and activity-dependent cofilin phosphorylation,[91] and showed loss at PSD in human AD brain.[11] F-actin is particularly associated by drebrin A at dendritic spines, postsynaptic sides of excitatory glutamatergic synapses. Drebrin A regulates the change of spine morphology, size, and density, presumably via regulation of actin cytoskeleton remodeling and dynamics.[92] The disappearance of drebrin may contribute to the spine loss in AD.[20] The actin-rich dendritic spine architecture is also modulated by neuronal cofilin.[93] The concentration of cofilin at PSD may regulate the efficacy of synaptic NMDA receptor[94] and dynamic reorganization of actin cytoskeleton in space and time.[95] Aβ peptides can induce the AD-like pathological change of ADF/cofilin–actin rods in vitro[96] and tau phosphorylation. Although, hyperphosphorylated tau is viewed as the major cytoskeletal protein pathology in AD, the phosphorylated neurofilament is another constituent of aggregates in AD brain.[97] Similar phosphorylated neurofilaments also occur in the neural inclusions, Lewy bodies, in DLB disease.[97,98]

Synaptic Cell-Adhesion Proteins

Synaptic adhesion proteins are not merely static structural components but are often dynamic regulators of synaptic function, participate in the formation, maturation, function, and plasticity of synapse, and control the number, location, and type of synapse. These cell-adhesion molecules (CAMs) include neuroligin, integrin, cadherin, Ephrins-EPH receptor, Nectin, NCAM, SynCAM, L1-CAM, and protocadherin. The known AD-relevant CAMs are summarized below.

Neuroligrin

Neurexin and neuroligin are synaptic cell-adhesion proteins. The neurexin and neuroligin junction connects presynaptic and postsynaptic neurons to form the synapse, mediates signaling across the synapse, and shapes the properties of neural network by specifying synaptic function. The neurexin and neuroligin junction selects binding to postsynaptic proteins PSD-95, GKAP, and Shank.[99] The protein level of postsynaptic neuroligin-1 is affected by apoE4, the major genetic risk factor for AD and other neurodegenerative diseases. The lower level of apoE4 protein could lead to the loss of postsynaptic neuroligin-1 in mice model.[100]

Integrin

Integrin-mediated communication regulates many cell physiological processes including cell cycles. The fibrils of Aβ effect on integrin/focal adhesion (FA) signaling pathways that mediate cell-cycle activation and cell death. The development of AD includes an extremely complicated change at the synaptic protein level. The pathological alteration of integrin/FAK/FA signaling pathway induced by fibrils of Aβ may alter neuronal viability and synaptic plasticity during the course of AD.[101]

N-Cadherin

Cadherins are transmembrane cell adhesion proteins. N-cadherin homophilic interactions connect pre- and postsynaptic membranes together.[102,103] N-cadherin, NMDA receptor, AMPA receptor GluR2/3, and PSD-95 and other synaptic proteins are integrated at spine; the dynamic alteration of N-cadherin modifies the plasticity of synaptic structure and function.[104-106] This dynamic change of N-cadherin is also mediated by the activities of NMDA receptor and presenilin-1(PS1).[107,108] PS1 binds cadherins and stabilizes the cadherin/catenin cell adhesion complexes at the plasma membrane.[109]

Ephrins-Eph Receptors

Ephrins and Eph receptors regulate excitatory neurotransmission and play a role in the morphological change of dendritic spine remodeling. The pathological changes of Ephrins and Eph receptors could be related to the AD development. EphA4 and EphB2 receptors were lost in the hippocampus at early stage of APP mutation AD mouse. A similar pathological change in Eph receptor levels was also observed in postmortem hippocampal tissue from incipient AD patients.[110]

Modulatory Enzymes

The PSD consists of hundreds of proteins beside the above reminded proteins. The PSD-associated protein kinase/phosphatase and other modulatory enzymes play multiple roles in the spine loss in AD development. These proteins include nonreceptor protein tyrosine kinase, Fyn[111]; CaMKII[33,112]; protein kinase C (PKC)[113]; mitogen activated kinase, Cdk5, GSK3β, Rho kinase (ROCK)[114]; p21-activated kinase[115]; calcineurin[116,117]; protein phosphatase I[118]; protein phosphatase 2A[119]; neuronal nitric oxide synthase[120]; ubiquitin proteasome system[11]; O-GlcNAc modification relevant enzymes[121]; and peptidyl-prolyl isomerase Pin1.[122] Although relevant, the current manuscript will not further discuss how these enzymes might affect the PSD structure and function in AD development.

Summary

The PSD is complicated and the current manuscript only summarizes some key points. The spatial-temporal pathological changes at the PSD protein network are likely to occur in early AD. The accumulation of these pathological changes could impact synaptic homeostasis leading to negative synaptic formation and synaptic loss and dysfunction. Animal AD models are limited because they do not show the full spectrum of pathological change seen in human AD. Most current studies of AD pathogenesis use human postmortem tissues and there is need for studies of the PSD in cases who die with early stage disease.

Declaration of Conflicting Interests

The author(s) declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research and/or authorship of this article: NIH1R21AG031388 (YG) and Potamkin Foundation (CFL).

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