Invited Mini Review

Synapses in neurodegenerative diseases

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Synapse is the basic structural and functional component for neural communication in the brain. The presynaptic terminal is the structural and functionally essential area that initiates communication and maintains the continuous functional neural information flow. It contains synaptic vesicles (SV) filled with neurotransmitters, an active zone for release, and numerous proteins for SV fusion and retrieval. The structural and functional synaptic plasticity is a representative characteristic; however, it is highly vulnerable to various pathological conditions. In fact, synaptic alteration is thought to be central to neural disease processes. In particular, the alteration of the structural and functional phenotype of the presynaptic terminal is a highly significant evidence for neural diseases. In this review, we specifically describe structural and functional alteration of nerve terminals in several neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD). [BMB Reports 2017; 50(5): 237-246]

INTRODUCTION

Synapse is a fundamental unit for brain function. Flow of neural information between neurons is ignited from presynaptic terminals by the release of a small chemical ingredient called neurotransmitter. This is stored in the small endosomal compartment (synaptic vesicle (SV)), and it's released by the fusion of SV, facilitated by a series of neuronal-activity triggered action of molecular players in the release area (active zone) at the presynaptic terminals.

The presynaptic terminal is composed of several structural and functional components. Cytomatrix proteins (Bassoon and Piccolo) and cytoskeletal protein (actin) provide the structural framework. The active zone (AZ) is the critical site for neurotransmitter release. Many essential molecular machineries are localized in the AZ, such as SNARE components for fusion, voltage-gated Ca^{2+} channels, cell adhesion molecules, etc. Each nerve terminal possesses around 100-200 synaptic vesicles. The synaptic vesicle (SV), a tiny endosomal compartment ($\sim$40 nm diameter), contains the neurotransmitter which associates directly and/or indirectly with more than a hundred proteins for proper functioning. For appropriate physiological functions, a number of proteins exist at the nerve terminals. Physiologically, the regulation and maintenance of neurotransmitter release remain critical questions. Several distinct SV pools distributed in the presynaptic terminal and SV exocytosis is tightly regulated by Ca^{2+} and its molecular players. Subsequently, SV retrieval continuously maintains the synaptic communication via several endocytic pathways. However, the morphological and physiological intact is easily altered in various neurological diseases. From synaptic vesicle and synaptic protein depletion to neurotransmission and Ca^{2+} dynamics impairment, a number of alterations in the structure and function of nerve terminals are exhibited in neurological diseases. Furthermore, these presynaptic dysfunctions are thought to be the very early symptoms of neuronal disorders.

This review specifically describes the structural and functional presynaptic alterations in neurodegenerative diseases. Alzheimer's disease (AD) is a high impact neurodegenerative disease. Several pathogenic factors have been identified, such as amyloid beta (Aβ) plaque, neurofibrillary tangle, and ApoE4. However, the exact pathological etiology requires to be further explored. It is important to understand synaptic alterations by these factors at the initial stage, before the eventual occurrence of neuronal cell death. Parkinson's disease (PD) is the second most common neurodegenerative disease, exhibiting degeneration of dopaminergic neurons in the substantia nigra pars compacta. Consequently, this results in dopamine depletion in the brain, leading to several neurological symptoms, tremors, bradykinesia, and rigidity. A number of sporadic and familial factors have been discovered. Some of the evidences have reported that these factors are deeply implicated with presynaptic function, although it is still much less known how PD is initiated. Other neurodegenerative diseases, such as Huntington disease (HD) and amyotrophic lateral sclerosis (ALS), are also involved in synaptic dysfunction. We describe in depth normal and pathological phenotype of these factors at presynaptic terminals.

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NERVE TERMINALS IN ALZHEIMER'S DISEASE

Alzheimer's disease (AD), the most common type of dementia, is a rapidly emergent and prominent neurodegenerative disease. The patient progressively loses their memory with a decline in cognition, eventually reaching mortality due to death of the brain cells. Several causative genetic factors have been revealed. Oligomerization of the amyloid beta (Aβ) plaque from amyloid precursor protein (APP) by BACE and γ-secretase, is a well-known factor for AD. Mutation or modification of the Tau protein aggregates to form neurofibrillary tangle (NFT) or paired helical filaments (PHF), called Tauopathy, which is also a known cause of AD. A critical genetic factor for late-onset AD is apolipoprotein E, particularly ε4 isoforms (ApoE4). Although these genetic factors are identified and characterized, a number of complicities are still emerging, and remain elusive. Here, we describe the genetic factors involved in the function and dysfunction at the presynaptic terminals (Table 1).

Amyloid precursor protein (APP) and Amyloid beta (Aβ)

Amyloid precursor protein (APP) is an essential source for amyloid beta 40 or 42 (Aβ 40 or 42) which are known major pathogenic factors in AD. APP normally participates in presynaptic function, although primary function of APP is still not explored. APP is enriched in nerve terminals with Rab5 positive large vesicular organelle (1) or a small set of synaptic vesicles (2), and is involved in structure and function of nerve terminals. APP modulates the initial nerve terminal formation. Cultured neurons from APP knock-out brain revealed upregulation of synaptophysin, a presynaptic marker. Consistently, immunohistochemistry from a slice of APP KO brain showed a high intensity of synaptophysin, indicating that APP is a negative regulator of synaptic formation. Secondly, APP is also involved in physiological modulation of synaptic functions.

APP KO neurons significantly increase the readily releasable pool (RRP) of synaptic vesicles (3). According to computational analysis of APP, it is likely to serve as a hub protein in the presynaptic active zone (PAZ), and is a context regulator in the hippocampal active zone network (4).

Amyloid beta (Aβ) is a fragment peptide from APP, cleaved by BACE and γ-secretase. Oligomeric aggregation of Aβ peptide is a critical pathogenic factor in AD. Several reports exhibit the Aβ tangle effects in nerve terminal phenotype. Treatment of Aβ oligomer in neurons results in significantly decreasing the presynaptic protein expression, but not post-synapse (5), indicating that Aβ affects the initial structural formation of presynaptic terminals. Physiologically soluble Aβ binds to APP, inducing the APP-APP homodimer. Consequently, there is a boost of Ca^{2+} influx, eventually resulting in an increase in the release probability (6, 7), indicating that Aβ is a positive regulator of neurotransmission at nerve terminal. However, in pathological conditions, increased Aβ can perturbs the release probability by altering spike probability of neurons (8). Internalized Aβ is localized at the nerve terminal, subsequently disrupting the synaptic vesicle protein VAMP2 function for vesicle fusion (9). In addition, it induces the depletion of presynaptic mitochondria and decreases its motility, thereby decreasing the size of synaptic vesicle pool.

Another important feature of the Aβ at synapses is that the synaptic activity for neurotransmission and release of Aβ is tightly correlated, and a nerve terminal is a major place for Aβ release. The brain interstitial fluid (ISF) reveals that synaptic activity influences the Aβ levels. The more the synaptic activity, higher is the Aβ level in ISF. This result correlates with APP endocytosis. The cleavage of APP to produce Aβ occurs in the endosomes or a small fraction of SV, and not on the surface of the plasma membrane (2). Synaptic vesicle exocytosis is thus required for more endocytosis of APP.

Table 1. Summary of presynaptic phenotype by AD genetic factors

	Alzheimer's disease	
Factor	Phenotype at presynaptic terminal	Ref
Amyloid Precursor Protein (APP)	• Negative regulator of synapse formation	3
	• Negative regulator for readily releasable pool of synaptic vesicle	3
	• Molecular Hub in presynaptic active zone (PAZ)	4
Amyloid beta (Aβ)	• Downregulation of presynaptic protein expression	5
	• Increase release probability (soluble Aβ- normal condition)	7
	• Disruption of vesicle fusion ability by inhibiting VAMP2 function (pathologic Aβ)	9
BACE1	• Negative regulator for excitatory synaptic transmission (homeostatic synaptic plasticity)	15
γ-secretase/Presenilin	• Presynaptic short-term plasticity, synaptic facilitation	17
	• Homeostatic synaptic scaling of excitatory synapses	18
Tau	• Synaptic stability (presynaptic proteins, synaptic vesicle)	19, 20
ApoE4	• Downregulation of amount glutamate	27
	• Modulation of spontaneous vesicle release	28

Hence, the production and release of Aβ are modulated by activity-dependent synaptic transmission and endocytosis at the nerve terminals (10, 11).

Beta-secretase (BACE)

β-site amyloid precursor protein-cleaving enzyme 1 (BACE1) is a key enzyme that produces Amyloid beta under pathological conditions. Localized at the synaptic vesicles, BACE1 is important for synaptic functions. Numerous potential substrates have been identified, which contain several synaptic proteins, in addition to APP (12). Furthermore, BACE1 was bio-chemically detected in the synaptic vesicle enriched fraction, indicating that synaptic vesicle is the likely location for APP processing (13, 14). BACE1 KO mice revealed that basal excitatory synaptic transmission was augmented. It is likely that the pathway downstream of BACE1 at the synapse was decreased, which could be due to the scaling of homeostatic synaptic plasticity (15). Synaptic adhesion protein Neuroligin1 and voltage-gated sodium channel were also known substrates for BACE1; however, it is as yet unknown how BACE1 regulates these substrates.

γ-secretase and presenilin

γ-secretase, along with BACE1, is essential for the production of a 42 peptide of amyloid beta. Several functions of γ-secretase have been reported at synapses. Localization studies revealed that γ-secretase is present in the synaptic endosomal fraction of rat brain, which is highly overlapped with the localization of BACE1 protein (16). In neurons with conditional knockout of presenilin, one of the subunits of the γ-secretase complex, presynaptic short-term plasticity and synaptic facilitation were severely altered, mainly mediated by presynaptic functions; these impairments result from intra-cellular Ca^{2+} release at the presynaptic terminals (17). In addition, hippocampal neurons derived from presenilin KO mice failed to the homeostatic scaling of excitatory synapses (18). Collectively, presenilin regulates neurotransmission at the nerve terminals.

Tau

Tau was originally discovered as a microtubule-associated protein. The neurofibrillary tangle (NFT) or paired helical filament (PHF) one of the major hallmarks of AD, is formed by Tau protein aggregation. However, studies report the func-tioning of tau at synapses. Tau is involved in axonal transport and synaptic protein stability for regulation of microtubule stability (19). In addition, it also provides the structural support to form and maintain synapses (20). Truncated tau contains specific phosphor-pattern, and can be localized both at the pre- and post-synaptic compartments. Particularly, at the presynaptic terminal, it impairs the stability of microtubules, resulting in a reduction of synaptic vesicles (21).

In pathological conditions, the Tau protein strongly influences synaptic dysfunction. The brain of the rTg4510 mouse, a human mutant P301L tau overexpressed mouse model, revealed age-dependent synaptic loss at both the pre- and post- synaptic regions, subsequently resulting in synaptic dysfunction. Tauopathy exhibits a strong impairment of synaptic transmission, and in combination with APP models, the synaptic impairment was aggravated, suggesting that the two pathological protein (Tau and APP) act in concert with synaptic function and dysregulation (22, 23).

Apolipoprotein (APOE)

ApoE is a lipoprotein mainly involved in the transport of lipoprotein, cholesterol, and lipid-related materials. It is well known that ApoE is strongly related to the pathology of AD, and is also associated with another AD factor, such as Amyloid-beta. Particularly, the apolipoprotein E4 (ApoE4) allele is the major causative allele of ApoE, having a functional role in nerve terminals. Hippocampal neurons with ApoE4 allele expression have a high sensitivity to environmental factors that lower the levels of presynaptic proteins such as synaptophysin (24, 25), although the synaptic area in the dentate gyrus increases (26). In addition, ApoE4 targets the replacement mice, showed down-regulation of glutaminase which converts the glutamine to glutamate, and up-regulation of the vesicular glutamate transporter. Consequently, neurons replaced with ApoE4 release decreased levels of glutamate at nerve terminals (27). Interestingly, this effect on presynaptic terminals appear to be restricted only in ApoE4 alleles, and not in other E2 and E3 alleles, thereby suggesting that structural and functional regulation is specifically influenced by the ApoE4 allele. Recently, it has been discovered that several ApoE receptors (e.g. Apoer2 and Vldlr) are expressed at the nerve terminal membranes. Reelin, a ligand for ApoE receptor, signaled a transient increase of intracellular Ca^{2+}, resulting in elevation of spontaneous vesicle release by VAMP7 mediated fusion (28).

Also, ApoE4 and amyloid beta were closely associated in AD pathogenesis. In a patient with AD, the ApoE4 was colocalized with oligomeric Aβ, and enhanced the synaptic localization of oligomeric Aβ. These findings suggest that ApoE4 is a stimulator for oligomeric Aβ toxicity for synapses (29). The proteomic response in nerve terminals is more susceptible than in the cell body, suggesting that ApoE has a nerve terminal region-specific functional effect.

NERVE TERMINALS IN PARKINSON'S DISEASE

Parkinson's disease (PD) is the second most common neuro-degenerative disorder. It is a movement disorder characterized by bradykinesia, postural instability, and rigidity, following the progressive loss of dopaminergic neurons in the midbrain. Pathogenesis of PD is classified into sporadic and familial cases, which develop due to environmental and genetic factors. About two dozen genetic factors of PD have been identified so far. Few genetic factors, including α-synuclein,

Table 2. Summary of presynaptic phenotype by PD genetic factors

	Parkinson's disease	
Factor	Phenotype at presynaptic terminal	Ref
α-synuclein	• Impairment of dopamine release in SNpc	38
	• Impairment of synaptic vesicle endocytosis and reclustering	39,40
	• Reduction of synaptic vesicle recycling pool	41
LRRK2	• Impairment of release and decreased DA uptake in SNpc	48
	• Impairment of synaptic endocytosis in presynaptic terminals	45
Parkin	• Reduction of dopamine release	55
	• Impairment of synaptic plasticity in striatal cells	53
PINK1	• Impairment of synaptic plasticity and release of dopaminergic neuron	62
DJ-1	• Defect of LTD through inhibitory effects of D2 receptor	68
Synaptojanin1	• Slowed endocytosis rate for small stimulation by defect of phosphatase activity	74,75
Endophilin	• Regulation of Parkin expression	76

LRRK2 (Leucine-rich repeat kinase 2), Parkin, PINK-1 (PTEN Induced Putative Kinase 1) and DJ-1, have been thoroughly researched in the pathogenesis of PD. Accumulating evidence shows that genetic factors of PD are associated with alteration of the synaptic functions (30, 31) (Table 2).

α-synuclein

α-synuclein is a small protein containing 140 amino acids, and contributes to early-onset PD (32). Generally, α-synuclein localizes at the presynaptic terminal. It is associated with synaptic vesicles, controlled synaptic vesicle trafficking, and SNARE complex formations at the nerve terminal (33-35). In pathological conditions, α-synuclein is implicated in the alteration of synaptic functions. Human α-synuclein overexpressing animal models show protein aggregations at the nerve terminals (36, 37), and overexpression of human α-synuclein by viral vector injection into substantia nigra in animal models leads to impaired dopamine release (38). Furthermore, neurotransmission inhibition might be related to the impairment of synaptic vesicle endocytosis (39) or synaptic vesicle reclustering after synaptic vesicle endocytosis (40). In addition, the overexpressing pathogenic mutants of α-synuclein (A30P and A53T) in primary midbrain neurons, led to abnormal neurite growth and reduced the recycling pool of synaptic vesicles (41). This evidence suggests that α-synuclein aggregation alters synaptic formation and functions.

LRRK2

LRRK2 is a large multidomain protein which includes kinase, GTPase, and protein-protein interaction domains. It is one of the prominent familial PD factors, particularly the gain-of-function mutant of LRRK2 (G2019S) is strongly associated with familial PD as well as sporadic PD (42, 43). Several studies report that LRRK2 is implicated in the structural and functional regulation of synapses through kinase-dependent mechanisms. It regulates the presynaptic and postsynaptic morphology by

the phosphorylation-dependent interaction of Futsch and 4E-BP in fly models (44). LRRK2 participates in synaptic vesicle endocytosis by phosphorylating endophilin (45), which is related with delayed endocytosis of synaptic vesicles, and subsequently affecting the neurotransmission impairment (46). LRRK2 also phosphorylates the NSF (N-ethylmaleimide-Sensitive Factor) D2 domain (Threonine 645), which plays a key role in SNARE complex disassembly after synaptic vesicle exocytosis. NSF phosphorylation by LRRK2 exhibits an elevated rate of SNARE disassembly (47). BAC transgenic animals for LRRK2 G2019S mutation, characterized by elevated kinase activity, show impairment of striatal dopamine release and a decrease of dopamine uptake, without dopaminergic neuron loss in the substantia nigra pars compacta (SNpc) (48). Furthermore, a neuron with LRRK2 G2019S expression shows elevated release probability with increased synaptic density (49), and altered glutamatergic synaptic plasticity (50).

Parkin

Parkin is an E3 ubiquitin ligase, and has an important role in cellular homeostasis due to its regulation of mitophagy and protein degradation. However, the loss-of-function mutation of Parkin is associated with juvenile-onset PD (51, 52). Parkin has been implicated in the modulation of synaptic functions. Parkin KO mice show decrease of evoked dopamine release in the striatum, and the striatal medium spiny neuron exhibit impairments of synaptic plasticity, which are long-term depression and long-term potentiation (53). Parkin also negatively regulates the number and strength of excitatory synapse (54), and neurotransmission is impaired by reduced AMPA receptor endocytosis due to loss of function of Parkin (55). Several studies report that functional loss of Parkin impaired degradation of synaptic proteins, including α-synuclein, synphilin-1, and CDCrel-1, thereby contribute to protein aggregation (56-58).

PINK1

Inherited nonsense and missense mutation of PINK1 (PTEN-induced putative kinase1) is a known early-onset familial PD factor (59). PINK1 has a N-terminal mitochondrial targeting motif and a conserved kinase domain (60), and is closely related to mitochondrial function and mitochondrial quality control (61). Pathologic mutation of PINK1 results in abnormal morphology of mitochondria. In addition, there is impairment of dopamine release, which presumably relates to synaptic mitochondrial dysfunction by pathogenic PINK1 (62). Loss of PINK1 also impairs the normal development of dopaminergic neuron, consequently leading to locomotor dysfunction (63). PINK1-deficient mice show normal number of dopaminergic neurons, but the release of dopamine is significantly decreased, suggesting that PINK1 has a role in synaptic transmission (64).

DJ-1

Generally, DJ-1 acts as a sensor for cellular redox homeostasis (65). However, functional mutation of DJ-1 is a causative familial factor for autosomal recessive early-onset PD (66). Localization studies reveal that DJ-1 is localized in the synaptic membrane. The binding affinity for synaptic membrane reduces with pathogenic DJ-1 compared to WT DJ-1 (67), indicating that it is likely involved in synaptic functions. In fact, DJ-1 depleted mice show signs of LTD (long-term depression), through the inhibitory effects of the D2 receptor by loss of DJ-1 (68).

Synaptojanin-1

Synaptojanin-1, a known phosphoinositide phosphatase, has a role in endocytosis process. It interacts with several endocytic proteins such as dynamin, Dap160/intersectin, and BAR proteins including endophilin and amphiphysin (69, 70), suggesting a key role in synaptic vesicle recycling processing, particularly clathrin-coated pit uncoating (71). Recently, the Sac1 domain mutation of synaptojanin-1 (p.Arg258Gln) has been reported in a family with early-onset progressive Parkinsonism (72, 73). Although synaptojanin-1 mutation mediated pathogenesis of PD has been less explored, the pathogenic phenotype is exhibited in mutations of synaptojanin-1 associated with PD, as well as early onset refractory seizures and neurological decline (74, 75), suggesting that the loss-of-function of synaptojanin-1 may contribute to the pathogenesis of PD and other neurological diseases by impaired synaptic vesicle recycling.

Endophilin

Endophilin is a key factor in synaptic vesicle recycling. Recently, however, some papers report that it is related to PD genetic factors, including LRRK2, parkin, and synaptojanin-1 (45, 76, 77). Endo-A, a fly ortholog of endophilin, is a substrate for LRRK2. BAR domain (Serine75) in Endo-A is phosphorylated, and recruitment of Endo-A to the endocytic complex during endocytosis gets modulated. Consequently, hyper-phosphorylation of BAR domain of Endo-A in LRRK2 G2019S mutant shows impairment of synaptic endocytosis in presynaptic terminals (45). In addition, endophilin phosphorylation by LRRK2 increases the recruitment of atg3 to the membrane area of presynaptic terminals, resulting in macroautophagy induction, affecting the membrane curvature induction for autophagy (78). Interestingly, endophilin mutant mice exhibited strongly increased parkin expression, suggesting that endophilin genetically interacts with parkin (76).

NERVE TERMINALS IN OTHER NEURODEGENERATIVE DISEASES

ALS

Amyotrophic lateral sclerosis (ALS) is a motor neuron disorder characterized by progressive loss of motor neurons in the cortex, brainstem and spinal cord. The loss of motor neuron leads to muscle atrophy and weakness, thereby eventually resulting in death. Superoxide dismutase-1 (SOD-1), one of the most prominent ALS genetic factors, is an antioxidant enzyme involved in the conversion of free superoxide radicals to oxygen and hydrogen peroxide. Both, a dominant and a recessive mutation of SOD-1, have been identified in ALS patients (79-81). It has been reported that the mutations of SOD-1 were implicated in synaptic dysfunctions. Both wild type of SOD-1 and pathogenic SOD-1 were localized at the pre and post-synapse. The G93A SOD-1 mutant, one of the pathogenic SOD-1 mutants, shows mislocalization in presynaptic terminals as well as post-synapse, thereby impairing axonal transport and contributing neuronal cell death (82, 83). SOD1 mutant mice also show length-dependent axonopathy with synaptic degeneration (84), and decreased synaptophysin-positive presynaptic bouton in the remaining motor neurons (85). Mutation of TDP-43, a DNA-/RNA-binding protein which modulates RNA splicing and micro RNA biogenesis (86, 87), has been identified in familial ALS. Transgenic animals of the mutant with human TDP-43 exhibit reduced levels of

Table 3. Summary of presynaptic phenotype by ALS and HD genetic factors

|		ALS and Huntington's disease	
	Factor	Phenotype at presynaptic terminal	Ref
ALS	SOD-1	• Axonal transport	83
		• Synaptic degeneration	84,85
	TDP-43	• Expression regulation of presynaptic protein	88
		• Attenuation of synaptic transmission	89
	FUS	• Active zone formation, synaptic transmission	93
HD	HTT	• Synaptic transmission, release probability	94
		• Synaptic vesicle dynamics	95,96
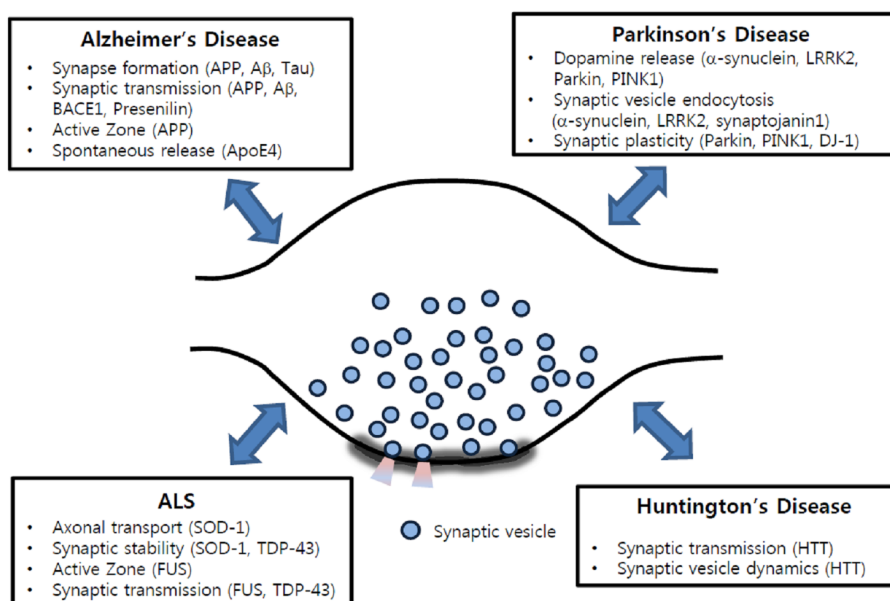
Fig. 1. Summarization of diagram for alteration of presynaptic terminals in various neurodegenerative diseases.

synaptophysin (a presynaptic protein) in the brain, as well as cognitive and motor deficits in behavioral tests (88); also, the synaptic transmission was attenuated (89). FUS (Fused-in-Sarcoma) is also one of the DNA/RNA-binding proteins having a similar structure and functions as TDP-43 (90). The mutation in nuclear localization signal (NLS) of FUS leads to increased cytoplasmic FUS position, which induces the aggregation of FUS mutants, as a pathogenesis of ALS (91, 92). FUS mutations were also linked to synaptic dysfunctions. Overexpression FUS mutant disrupts formation of presynaptic active zones, consequently reducing the synaptic transmission with decreased quantal size (93) (Table 3).

Huntington's disease

Huntington's disease (HD) is an inherited autosomal dominant neurodegenerative disorder. It is mainly caused by mutation of the huntingtin (htt) protein, which has an abnormally high copy of polyglutamine (polyQ) repeat at the N-terminus. General symptoms of HD are motor dysfunction and cognitive deficits, which correlate with the neurodegeneration of specific regions such as the striatum and cerebral cortex. Some of the presynaptic alterations in HD have been reported in various genetic models. An HD model system expressing 128 polyQ expansion in Drosophila, revealed that it had significantly higher neurotransmitter release and release probability (94). Presynaptic specific protein alterations are also reported. For example, rabphilin 3A expression level decreased (95); however, levels of SCAMP5, one of the synaptic vesicle proteins was increased (96), suggesting that these alterations of presynaptic protein levels result in an impairment of synaptic vesicle fusion or endocytosis process (Table 3).

CONCLUSION

We here reviewed the structural and functional alterations of presynaptic terminals by genetic factors in several neuro-degenerative diseases (Fig. 1). In AD, APP, an original source for Aβ peptide, is a molecular hub in PAZ. It negatively regulates the nerve terminal formation and readily releasable synaptic vesicle pool. Pathological Aβ (aggregate Aβ) strongly inhibits the synaptic vesicle fusion machinery; however, soluble Aβ increases the release probability. BACE1 and presenilin are also important regulators for presynaptic physiology. In addition, other genetic factors for AD (Tau and ApoE4) are also involved in synaptic stability and synaptic release. In PD, numerous studies for the genetic factors has revealed the implication in presynaptic functions. α-synuclein expression controlled the release probability and recycling pool size, and LRRK2 modulates dopamine release and synaptic vesicle endocytosis by phosphorylating several endocytic proteins (e.g. endophilin). Interestingly, recently accumulating reports show that endocytic proteins (e.g. synaptojanin1, endophilin) are strongly related in PD, indicating that the synaptic vesicle endocytosis process might be an important pathway related in the pathogenesis of PD.

A number of the genetic factors for neurodegenerative diseases are closely related with synaptic function and its alteration. However, most studies just display the phenotype of synaptic dysfunctions, without detailed mechanisms of how the genetic factors result in these dysfunctions. By far, most studies for the pathogenesis of neurodegenerative diseases tend to focus on mechanisms of how neuronal cell death or neurodegeneration occur. Most of the neurodegenerative diseases are generally thought to be chronic diseases.

Ultimately, neurons are likely to die after experiencing a number of abnormal processes during neurodegeneration. Synapses possess high variability and plasticity, and are also highly vulnerable to pathological conditions. It is likely to reveal abnormal phenotype or alteration of the synaptic function at the early onset of neurodegeneration, suggesting that an in depth investigation for synaptic dysfunction may provide a new approach to the understanding of the early pathogenesis of neurodegenerative diseases.

ACKNOWLEDGEMENTS

CONFLICTS OF INTEREST

The authors have no conflicting financial interests.

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