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ABSTRACT

Synapse is a basic structural and functional component for neural communication in the brain. To initiate and maintain continuous functional neural information flow, the presynaptic terminal is a structurally and functionally essential place as an initiator for communication. It contains synaptic vesicles (SV) filled with neurotransmitter, active zone for release place, and a number of proteins for SV fusion and retrieval. The structural and functional synaptic plasticity is one of the representative characteristics however it is also highly vulnerable in various pathological circumstances. In fact, synaptic alteration is thought to be central to the neural disease process. In particular alteration of the structural and functional phenotype of the presynaptic terminal is one of the most 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).

INTRODUCTION

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

Presynaptic terminal is composed of several structural and functional components. Cytomatrix proteins (Basson and Piccolo) and cytoskeletal protein (actin) provide a structural framework. Active zone (AZ) is a critical area as the site for neurotransmitter release. Many of essential molecular machinery are localized in AZ such as SNARE components for fusion, voltage-gated Ca^{2+} channels, cell adhesion molecules and so on. Each nerve terminal possesses around 100~200 synaptic vesicles. Synaptic vesicle (SV), a tiny endosomal compartment (~40nm diameter), contains neurotransmitter and it associates directly and/or indirectly with more than a hundred proteins for its proper function. As such a number of proteins are placed in nerve terminals for appropriate physiological function. Physiologically, how neurotransmitter release is regulated and maintained are critical questions. Several distinct SV pools distributed in presynaptic terminal and SV exocytosis is tightly regulated by Ca^{2+} and its molecular players. Subsequently, SV retrieval occurs to continuously maintain synaptic communication via several endocytic pathways. However, morphological and physiological intact can be easily altered in various neurological diseases. From synaptic vesicle and synaptic protein depletion to neurotransmission and Ca^{2+} dynamics impairment, a number of alteration in the aspect of structure and function of nerve terminal can be exhibited in neurological disease. Furthermore, these presynaptic dysfunctions are thought to be the very early symptoms of neuronal disorders.

In this review, we specifically describe structural and functional presynaptic alteration in

neurodegenerative diseases. Alzheimer's disease (AD) is one of the highest impact neurodegenerative diseases. Several pathogenic factors were identified such as amyloid beta (Aβ) plaque, neurofibrillary tangle, and ApoE4. However exact pathological etiology still need to be more explored. It is important understanding synaptic alteration by these factors at the very initial stage before eventually occurring neuronal cell death. Parkinson's disease (PD) is the second most common neurodegenerative disease. It's been known degeneration of dopaminergic neurons in the substantia nigra pars compacta. Consequently, it causes dopamine depletion in the brain, which causes several neurological symptoms, tremor, bradykinesia, 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 unknown how PD is initially developed. Other neurodegenerative diseases Huntington disease (HD), amyotrophic lateral sclerosis (ALS) are also involved in synaptic dysfunction. We describe in depth normal and pathological phenotype of these factors at presynaptic terminals.

1. **Nerve terminals in Alzheimer's disease**

Alzheimer's disease (AD), the most common type of dementia, is fast growing and one of the most prominent neurodegenerative diseases. It progressively loses the memory and decline cognition and eventually it reach to die because of the death of brain cells. Several causative genetic factors have been revealed. Oligomerization of 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 Tau protein can aggregate to form neurofibrillary tangle (NFT) or paired helical filaments (PHF), called Tauopathy, which is also known one of the causative facts 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 remained elusive. Here we describe these genetic factors regarding function and dysfunction in presynaptic terminals.

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

Amyloid precursor protein or APP is an essential source for amyloid beta 40 or 42 (Aβ 40 or 42) which are known as one of the major pathogenic factors in AD. APP normally participates in presynaptic function, although primary function of APP is still not much explored. APP is enriched in nerve terminals with Rab5 positive large vesicular organelle (1) or small set of synaptic vesicles (2) and involved in structure and function of nerve terminals. Firstly APP modulates nerve terminal formation. Cultured neurons from APP knock-out brain revealed up-regulate of synaptophysin, a presynaptic marker. Consistently, immunohistochemistry from a slice of APP KO brain showed the high intensity of synaptophysin indicating that APP is a negative regulator of synaptic formation. Secondly, it is also involved in physiological modulation of synaptic function. APP KO neurons significantly increased readily releasable pool (RRP) of synaptic vesicle (3). According to computational analysis of APP, it is likely to serve as a hub protein in the presynaptic active zone (PAZ) and it is context regulator in 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 one of the critical pathogenic factors in AD. Several reports exhibited Aβ tangle had affected in nerve terminal phenotype. Treatment of Aβ oligomer in neurons resulted significantly in decreased presynaptic protein expression but not post-synapse (5) indicating that Aβ initially affects the structural formation of presynaptic terminals. Physiologically soluble Aβ bound APP and that induced APP-APP homodimer. Consequently, it caused boosting of Ca^{2+} influx, eventually release probability was increased

(6, 7) indicating that Aβ is a positive regulator of neurotransmission at nerve terminal. However in a pathological condition, increased Aβ can also perturb release probability by altering spike probability of neurons (8). Internalized Aβ was localized to nerve terminal, subsequently disrupted synaptic vesicle protein VAMP2 function for vesicle fusion (9). In addition, it induced depletion of presynaptic mitochondria and its motility and decreased the size of synaptic vesicle pool.

Another important point regarding Aβ at synapses is that 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) revealed that synaptic activity influence Aβ level. The more synaptic activity was the higher Aβ level in the ISF. This result is also correlated with APP endocytosis. Because cleavage of APP to produce Aβ occurred in endosomes or a small fraction of SV, not in the surface of the plasma membrane (2). And synaptic vesicle exocytosis was required for more endocytosis of APP. Thus production and release of Aβ are modulated by activity-dependent synaptic transmission and endocytosis at nerve terminals (10, 11).

1.2. Beta-secretase (BACE)

β-site amyloid precursor protein-cleaving enzyme 1(BACE1) is a key enzyme to produce Amyloid beta in the pathological condition. However, BACE1 itself is also important for synaptic function since BACE1 was localized synaptic vesicles and more than dozens of the potential substrate had been identified, which contained several synaptic proteins in addition to APP (12). Furthermore, biochemically BACE1 was detected in the fractionation of synaptic vesicle enriched fraction, indicating that synaptic vesicle is likely the place for APP processing (13, 14). BACE1 KO mice revealed that basal excitatory synaptic transmission

was augmented. It is likely that downstream of BACE1 at synapse was decreased, which resulted from scaling of homeostatic synaptic plasticity (15). Synaptic adhesion protein Neuroligin1 and voltage-gated sodium channel were also known substrates for BACE1 however it is still not known how these substrates are functionally regulated by BACE1.

1.3. γ-secretase and presenilin

γ-secretase is an essential member for Aβ40, 42 peptide production by cooperating with BACE1. Several functions of γ-secretase or presenilin, one of the subunits in γ-secretase complex at synapses were reported. The localization study revealed that γ-secretase had found in synaptic endosomal fraction of rat brain which is highly overlapped with the localization of BACE1 protein (16). In neurons with conditional knockout of presenilin, presynaptic short-term plasticity and synaptic facilitation were severely altered, which are mainly mediated by presynaptic functions and these impairments resulted from intracellular Ca^{2+} release in 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 in nerve terminals.

1.4. Tau

Tau has originally discovered as a microtubule-associated protein. It has been known that neurofibrillary tangle (NFT) or paired helical filament (PHF), one of the major hallmarks of AD is formed by Tau protein aggregation. However, it is reported that tau had functioned at synapses. Due to regulate microtubule stability, it participated in axonal transport and synaptic protein stability (19). In addition, it also provided structural support to form and maintain synapses (20). Truncated tau which contained specific phosphor-pattern can be localized both pre- and post-synaptic compartment. Particularly in presynaptic terminal, it

impaired the stability of microtubule, which caused reduction of synaptic vesicles (21).

In pathological condition, Tau protein strongly influenced synaptic dysfunction. The brain of the rTg4510 mouse, human mutant P301L tau overexpressed mouse model, revealed age-dependent synaptic loss both pre- and post- synaptic region and resulted in synaptic dysfunction. Tauopathy exhibited strong impairment of synaptic transmission and in combined with APP models synaptic impairment was aggravated, suggesting that two pathological protein both Tau and APP act in concert with synaptic function and dysregulation (22, 23).

1.5. Apolipoprotein (APOE)

ApoE is a lipoprotein that mainly involves in the transport of lipoprotein, cholesterol, and lipid-related materials. It has been known that ApoE is heavily related to the pathology of AD and correlated with another AD factor such as Amyloid-beta. Particularly, the apolipoprotein E4 (ApoE4) allele is a major form of a causative allele in ApoE. It also has a functional role in nerve terminals. Hippocampal neurons with ApoE4 allele expression had high sensitivity to an environmental factor that caused a lower level of presynaptic proteins such as synaptophysin. (24, 25), although the synaptic area in the dentate gyrus was increased (26). In addition to that, ApoE4 targeted replacement mice showed down-regulation of glutaminase which converted glutamine to glutamate, and up-regulation of vesicular glutamate transporter. Consequently, neuron replaced with ApoE4 released decrease level of glutamate at nerve terminals (27). Interestingly, this effect on presynaptic terminals appeared restrictively only in ApoE4 allele but no other E2 and E3 allele, suggesting that structural and functional regulation is specifically influenced by particular ApoE4 allele. Recently it has discovered that several ApoE receptors (e.g. Apoer2 and Vldlr) were expressed at nerve terminal membrane. 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). ApoE4 also had a cooperative pathological behavior with amyloid beta in AD. In a patient with ApoE4 AD, apolipoprotein E4 was colocalized with oligomeric Aβ and enhanced synaptic localization of oligomeric Aβ. These 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.

2.**Nerve terminals in Parkinson's disease**

Parkinson's disease (PD) is the second common neurodegenerative disorder. It is known as a movement disorder characterized by bradykinesia, postural instability, and rigidity following the progressive loss of dopaminergic neuron in the midbrain. Pathogenesis of PD can be classified into sporadic and familial case developed by environmental and genetic factors. About two dozen genetic factors of PD have been identified by far, however a few genetic factors including α-synuclein, LRRK2 (Leucine-rich repeat kinase 2), Parkin, PINK-1 (PTEN Induced Putative Kinase 1) and DJ-1 were heavily studied primarily in pathogenesis of PD, Accumulating evidence has shown that the genetic factors of PD are associated with alteration of synaptic functions (30, 31).

2.1. α-synuclein

α-synuclein is a small protein, which is containing 140 amino acid and contributes to early-onset PD (32). Generally α-synuclein localizes at presynaptic terminal. It associated with synaptic vesicles and controlled synaptic vesicle trafficking and SNARE complex formation in nerve terminal (33-35). In the pathological conditions, α-synuclein has been implicated in

alteration of synaptic functions. Human α-synuclein overexpressing animal models showed the protein aggregations in nerve terminals (36, 37) and overexpression of human α-synuclein by viral vector injection into substantia nigra in animal models led to impaired dopamine release (38). And inhibition of neurotransmission might be related to the impairment of synaptic vesicle endocytosis (39) or synaptic vesicle reclustering after synaptic vesicle endocytosis (40). In addition, overexpression pathogenic mutants of α-synuclein (A30P and A53T) in primary midbrain neurons led to abnormal neurite growing and reduced recycling pool of synaptic vesicles (41). This evidence suggests that α-synuclein aggregation alters synaptic formation and functions.

2.2. LRRK2

LRRK2 is a large multidomain protein including kinase, GTPase, and protein-protein interaction domains. It is one of the prominent familial PD factors, particularly gain-of-function mutant of LRRK2 (G2019S) was strongly associated with familial PD as well as sporadic PD (42, 43). Several studies had reported that LRRK2 is implicated in the structural and functional regulation of synapses through kinase-dependent mechanisms. It regulated presynaptic and postsynaptic morphology by the phosphorylation-dependent interaction of Futsch and 4E-BP in fly models (44). LRRK2 participated in synaptic vesicle endocytosis by phosphorylating endophilin (45), which is related with delayed endocytosis of synaptic vesicles, and subsequently affected neurotransmission impairment (46). LRRK2 also phosphorylated 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 exhibited an elevated rate of SNARE disassembly (47). BAC transgenic animals for LRRK2 G2019S mutation characterized by elevated kinase activity showed 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 showed elevated release probability with increased synaptic density (49) and altered glutamatergic synaptic plasticity (50).

2.4. Parkin

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

2.5. PINK1

Inherited nonsense and missense mutation of PINK1 (PTEN-induced putative kinase1) is a known early-onset familial PD factor (59). It has an N-terminal mitochondrial targeting motif and a conserved kinase domain (60). PINK1 was closely related to mitochondrial function, and mitochondrial quality control (61). Pathologic mutation of PINK1 showed the abnormal morphology of mitochondria. In addition, it also showed impairment of dopamine release, which presumably related in synaptic mitochondrial dysfunction by pathogenic PINK1 (62). Loss of PINK1 impaired normal development of dopaminergic neuron. Consequently, it

revealed locomotor dysfunction (63). PINK1-deficient mice showed a normal number of dopaminergic neurons, however, evoked release of dopamine was significantly decreased suggesting that PINK1 has a role in synaptic transmission (64).

2.6. DJ-1

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

2.7. Synaptojanin-1

Synaptojanin-1 known as a 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 that it plays a key role in synaptic vesicle recycling processing particularly clathrin-coated pit uncoating (71). Recently, 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 yet, pathogenic phenotype exhibited that the 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 pathogenesis of PD and other neurological diseases by impaired synaptic vesicle recycling.

2.8.Endophilin

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

3. Nerve terminals in other neurodegenerative diseases

3.1. ALS

Amyotrophic lateral sclerosis (ALS) is a motor neuron disorder characterized by progressive loss of motor neuron in the cortex, brainstem and spinal cord. The loss of motor neuron leads to muscle atrophy and weakness, thereby eventually it leads to 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 had been identified in ALS patients (79-81). It had 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 in pre and post-synapse. The G93A SOD-1 mutant one of pathogenic SOD-1 mutant showed mislocalization in presynaptic

terminals as well as post-synapse, thereby impairing axonal transport and contributing neuronal cell death (82, 83). SOD1 mutant mouse also showed length-dependent axonopathy with synaptic degeneration (84) and decreased synaptophysin-positive presynaptic bouton in the remaining motor neuron (85). TDP-43 a DNA-/RNA-binding protein which modulates RNA splicing and micro RNA biogenesis (86, 87) were identified in familial ALS. Transgenic animals of the mutant with human TDP-43 exhibited a reduced level of synaptophysin, a presynaptic protein, in the brain as well as cognitive and motor deficit in behavior tests (88), and synaptic transmission was attenuated (89). FUS (Fused-in-Sarcoma) is also one of the DNA/RNA-binding proteins and have similar structure and functions in comparison with TDP-43 (90). The mutation in nuclear localization signal (NLS) of FUS led to increased cytoplasmic FUS position, which induced aggregation of FUS mutants as a pathogenesis ALS (91, 92). FUS mutations were also linked to synaptic dysfunctions. Overexpression FUS mutant disrupted formation presynaptic active zones, consequently reduced synaptic transmission with decreased quantal size (93).

3.2. Huntington's disease

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

of the synaptic vesicle proteins was increased (96) suggesting that these alterations of presynaptic protein level results in impairment of synaptic vesicle fusion or endocytosis process.

CONCLUSION

We here review structural and functional alteration of presynaptic terminals by genetic factors in several neurodegenerative diseases. In AD, APP an original source for Aβ peptide is a molecular hub in PAZ. It negatively regulated nerve terminal formation and readily releasable synaptic vesicle pool. Pathological Aβ (aggregate Aβ) strongly inhibited synaptic vesicle fusion machinery however soluble Aβ increased release probability. BACE1 and presenilin were also the important regulators for presynaptic physiology. In addition to that, other genetic factors for AD Tau and ApoE4 were also involved in synaptic stability and synaptic release. In PD, numerous studies for the genetic factors of PD had also shown the implication in presynaptic functions. α-synuclein expression controlled release probability and recycling pool size, and LRRK2 modulated dopamine release and synaptic vesicle endocytosis by phosphorylating several endocytic proteins (e.g. endophilin). Interestingly recently accumulating reports showed that endocytic proteins (e.g. synaptojanin1, endophilin) were strongly related in PD, indicating that synaptic vesicle endocytosis process might be an important pathway related with the pathogenesis of PD.

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

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

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FIGURE LEGENDS

Figure 1. Summarization of diagram for alteration of presynaptic terminals in various neurodegenerative diseases

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Figure1.

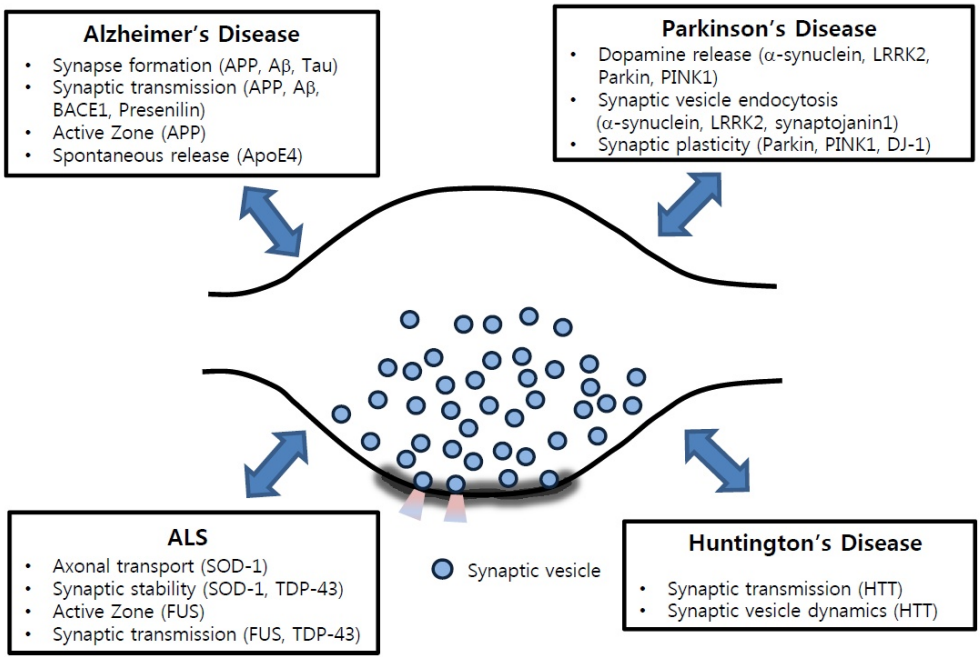
Alzheimer's Disease
Synapse formation (APP, Aβ, Tau)
Synaptic transmission (APP, Aβ, BACE1, Presenilin)
Active Zone (APP)
Spontaneous release (ApoE4)
Parkinson's Disease
Dopamine release (α-synuclein, LRRK2, Parkin, PINK1)
Synaptic vesicle endocytosis (α-synuclein, LRRK2, synaptojanin1)
Synaptic plasticity (Parkin, PINK1, DJ-1)
ALS
Axonal transport (SOD-1)
Synaptic stability (SOD-1, TDP-43)
Active Zone (FUS)
Synaptic transmission (FUS, TDP-43)
Synaptic vesicle
Huntington's Disease
Synaptic transmission (HTT)
Synaptic vesicle dynamics (HTT)

Table1. 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 • Negative regulator for readily releasable pool of synaptic vesicle • Molecular Hub in presynaptic active zone (PAZ)	3 3 4
Amyloid beta (Aβ)	• Downregulation of presynaptic protein expression • Increase release probability (soluble Aβ- normal condition) • Disruption of vesicle fusion ability by inhibiting VAMP2 function (pathologic Aβ)	5 7 9
BACE1	• Negative regulator for excitatory synaptic transmission (homeostatic synaptic plasticity)	15
γ-secretase / Presenilin	• Presynaptic short-term plasticity, synaptic facilitation • Homeostatic synaptic scaling of excitatory synapses	17 18
Tau	• Synaptic stability (presynaptic proteins, synaptic vesicle)	19, 20
ApoE4	• Downregulation of amount glutamate • Modulation of spontaneous vesicle release	27 28

Table2 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 • Impairment of synaptic vesicle endocytosis and reclustering • Reduction of synaptic vesicle recycling pool	38 39,40 41
LRRK2	• Impairment of release and decreased DA uptake in SNpc • Impairment of synaptic endocytosis in presynaptic terminals	48 45
Parkin	• Reduction of dopamine release • Impairment of synaptic plasticity in striatal cells	55 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

Table3. 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 • Synaptic degeneration	83 84,85
	TDP-43	• Expression regulation of presynaptic protein • Attenuation of synaptic transmission	88 89
	FUS	• Active zone formation, synaptic transmission	93
HD	HTT	• Synaptic transmission, release probability • Synaptic vesicle dynamics	94 95,96