



REVIEW

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Neurodegenerative changes initiated by presynaptic dysfunction

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Abstract

α -Synucleinopathies are a subgroup of neurodegenerative diseases including dementia with Lewy bodies (DLB) and Parkinson's disease (PD). Pathologically, these disorders can be characterized by the presence of intraneuronal aggregates composed mainly of α -synuclein (α Syn), which are called Lewy bodies and Lewy neurites. Recent report showed that more than 90% of α Syn aggregates are present in the form of very small deposits in presynaptic terminals of the affected neurons in DLB. However, the mechanisms responsible for presynaptic accumulation of abnormal α Syn remain unclear. In this article, we review recent findings on the involvement of presynaptic dysfunction in the initiation of neuronal dysfunctional changes. This review highlights that the presynaptic failure can be a potential trigger of the dying-back neuronal death in neurodegenerative diseases.

Introduction

Neurodegenerative diseases are age-associated and progressive disorders, which detrimentally affect patients' quality of life. Medical remedies that can fully cure the diseases are currently unavailable and invention of novel therapeutic applications is urgently required. Accordingly, it is important to identify the initial trigger(s) of the pathophysiological alterations in these diseases.

α -Synucleinopathies are a subgroup of neurodegenerative diseases including dementia with Lewy bodies (DLB), Parkinson's disease (PD), and multiple system atrophy (MSA). Pathological hallmark of these disorders is the formation of intracellular aggregates composed mainly of α -synuclein (α Syn), which are called Lewy bodies and Lewy neurites [1-3]. Pathological examination of DLB patients has identified the presence of abnormal α -synuclein (α Syn) aggregates in the presynaptic terminals [4-6]. However, the mechanisms responsible for presynaptic accumulation of abnormal α Syn remain elusive.

Role of α Syn in SNARE formation

α Syn is abundantly localized in the presynaptic nerve terminals [7,8]. The physiological functions of α Syn have yet to be defined, while several lines of evidence implicated this protein in the modulation of neurotransmitter

release through the regulation of soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex formation [9-11] and size of synaptic vesicle pool [12-15]. Vesicle-associated membrane protein-2 (VAMP-2) present in the synaptic vesicles, and syntaxin and synaptosomal-associated protein of 25 KDa (SNAP-25) in the presynaptic plasma membrane form the core SNARE complex, which regulate docking and fusion of synaptic vesicles to the presynaptic membrane [16]. A recent study showed the physical interaction of α Syn with VAMP-2 promotes SNARE assembly [10]. Cysteine-string protein- α (CSP α) also participates in SNARE assembly and mutant mice lacking CSP α displayed impaired SNARE formation and premature death, but both of these phenotypes are counteracted by transgenic expression of α Syn [9,17]. On the other hand, overexpression of α Syn with no overt toxicity inhibits neurotransmitter release, due to a defective reclustering of synaptic vesicles after endocytosis [15]. Additionally, overexpressed α Syn indirectly inhibits SNARE-mediated exocytosis by sequestering arachidonic acid, which up-regulates syntaxin and enhances its engagement with SNARE complex [11]. Importantly, abnormal redistribution of SNARE proteins has been observed in human PD patients and mice overexpressing a truncated form of human α Syn, which showed decreased release of dopamine (DA) in the striatum [18]. Therefore, presynaptic SNARE dysfunction is considered an initial pathogenic event in α -synucleinopathies.

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Accumulation of α -synuclein triggered by presynaptic dysfunction

In our recent study, we investigated the effects of SNARE dysfunction on endogenous α Syn using *Snap25*^{S187A/S187A} mutant mice [19]. These mice have homozygous knock-in gene encoding unphosphorylatable S187A-substituted SNAP-25. *Snap25*^{S187A/S187A} mutant mice present a concomitant reduction of neurotransmitter release, including serotonin and DA, from the amygdala, and develop convulsive seizures and anxiety-related behavior in general activity and light-and-dark preference tests [20]. We found that the mutant mice displayed a significant age-dependent change in the distribution of α Syn and its Ser¹²⁹-phosphorylated form in abnormally hypertrophied glutamatergic nerve terminals in the striatum. Electron microscopic analysis revealed the atypically condensed synaptic vesicles with concomitant mislocalization of α Syn protein to the periaxial zone in the glutamatergic nerve terminals (Figure 1). However, the *Snap25*^{S187A/S187A} mutant mice harbored no abnormalities in the nigrostriatal dopaminergic neurons [19]. Our results suggest that SNARE dysfunction is the initial trigger of mislocalization and accumulation of α Syn, and probably underlies the pathomechanism of α -synucleinopathies.

Effect of SNAP-25 dysfunction

Previous studies using neural preparations showed that the neurotransmitter release is regulated by protein kinase C, which phosphorylates Ser¹⁸⁷ residue in SNAP-25, augmenting exocytosis of synaptic vesicles [21,22]. Patch-clamp analysis showed chromaffin cells that overexpressed the S187A mutant form of SNAP-25 had impaired rate of presynaptic vesicle pool refilling [23]. Recently, we

reported that *Snap25*^{S187A/S187A} mice showed reduced DA and serotonin release in amygdala [20]. In human DLB brains, more than 90% of α Syn aggregates are located in the presynaptic terminals in the form of small deposits [4-6]. This is consistent with our findings of abnormal accumulation of α Syn in presynapses [19], suggesting that this process is the initial pathological event in DLB, eventually leading to the death and degeneration of neuronal cells [24]. Another finding that lends support to the role of α Syn aggregates in the presynaptic terminals in DLB is the lack of histopathological changes in the dopaminergic terminals in our study [19].

Role of α Syn in nerve terminals

In experiments on glutamate release conducted in hippocampal slices prepared from α Syn knockout mice [25], paired-pulse facilitation was significantly weaker, and high-frequency-induced long-term potentiation and frequency facilitation were not observed. These findings suggest that α Syn contributes to mobilization of glutamate-containing vesicles from the reserve pool [25]. α Syn may act as a positive regulator of neurotransmitter release at presynaptic terminals. Therefore, presynaptic accumulation of α Syn observed in our *Snap25*^{S187A/S187A} mice might reflect a compensatory response to a possible SNARE dysfunction-related chronic shortage of neurotransmitter release in the VGLUT1-positive nerve terminals [19].

Relation between glutamatergic and dopaminergic nerve terminals in the striatum

In the striatum, the medium spiny neurons, which constitute more than 90% of all striatal neurons, receive

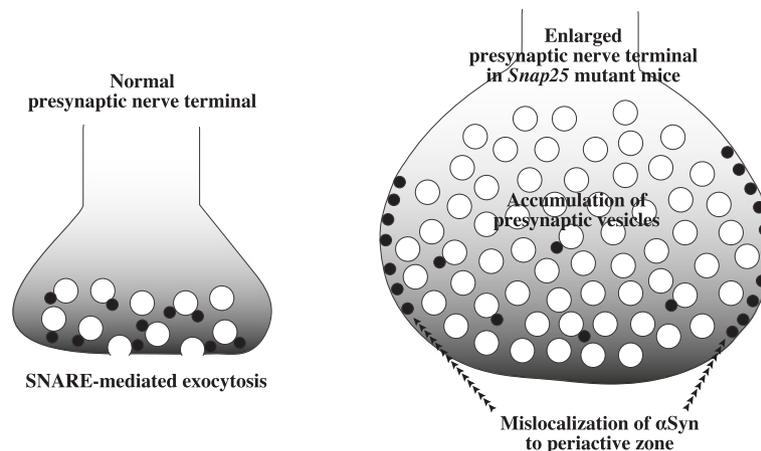


Figure 1 A hypothetical diagram showing enlarged presynaptic nerve terminals in SNAP-25 mutant mice. Normal presynaptic nerve terminals with uniform distribution of vesicles were observed in wild type mice while abnormally enlarged presynaptic nerve terminals with condensed synaptic vesicles and predominant localization of α Syn proteins in the periaxial zones were found in SNAP-25 mutant mice, suggesting that SNARE dysfunction leads to presynaptic accumulation of endogenous α Syn and perturbations to the finely-tuned balance between exocytosis and endocytosis.

input from glutamatergic axons that contact the spine head and dopaminergic axons that synapse with the dendritic spine neck. DA released from dopaminergic axons regulates the release of glutamate via D₂-like receptors on the corticostriatal nerve terminals [26,27]. We found no significant changes in the striatal tissue levels of DA and its metabolites in *Snap25*^{S187A/S187A} mice. These findings confirmed the results reported in our previous study using the same mouse model, in which the microdialysis analysis revealed marked reduction of DA release from the amygdala [20]. In another *in vitro* study using PC12 cells, phosphorylation of SNAP-25 at S187 potentiated calcium-dependent DA release and recruitment of synaptic vesicles containing DA [28-30]. These observations suggest decreased striatal DA release in *Snap25*^{S187A/S187A} mice, resulting in increased demand for neurotransmitter release at glutamatergic nerve terminals. Thus, presynaptic accumulation of αSyn might reflect a possible compensatory response to low DA inhibitory control over cortical glutamatergic drive.

Correlation of VAMP-2 with αSyn

Increased expression of VAMP-2 protein accompanied increased αSyn expression in the striatum of *Snap25*^{S187A/S187A} mice [19]. Binding of the carboxy terminus of αSyn to the amino terminus of VAMP-2 primes subsequent SNARE complex assembly [31]. Therefore, the increased VAMP-2 level might also reflect a compensatory response to the impaired synaptic vesicle release by enhancing SNARE complex formation in concert with increased αSyn.

Pathological changes in glutamatergic nerve terminals

Presynaptic neurotransmitter release is mediated by the synaptic vesicle cycle, consisting of exocytosis followed by endocytosis and recycling. Exocytosis incorporates synaptic vesicles into the presynaptic terminal membranes and increases the surface area, while endocytosis retrieves excess plasma membrane components followed by recycling to form other synaptic vesicles. Under normal conditions, the dynamics of balance between exocytosis and endocytosis are well preserved to maintain the correct surface area of the presynaptic terminal [32,33]. However, a mutant leucine-rich repeat kinase 2 (LRRK2) bacterial artificial chromosome (BAC) transgenic mouse model showed enlarged axonal endings in the striatal dopaminergic neurons, suggesting imbalance between exocytotic membrane addition and endocytic retrieval [34]. Excessive accumulation of presynaptic vesicles and enlargement of the VGLUT1-positive nerve terminals was also observed in *Snap25*^{S187A/S187A} mice [19]. Taking into consideration the synaptic vesicle cycle, our findings suggest that the balance of the cycle is likely biased toward decreased endocytosis.

The enlarged VGLUT1-positive nerve terminals of *Snap25*^{S187A/S187A} mice showed concomitant accumulation of αSyn and p-αSyn [19]. Kramer and Schulz-Schaeffer [5] have previously reported that 90% or even more of αSyn aggregates in DLB cases were located at the presynapses in the form of very small deposits. In parallel, dendritic spines were retracted, whereas the presynapses were relatively preserved, suggesting that neurotransmitter deprivation may explain the cognitive impairment in DLB [5,6]. While the presynaptic aggregates did not contain much p-αSyn in their examination [5,6], widespread varicosities and dot-like structures containing p-αSyn are commonly observed in αSyn-transgenic mouse model and human DLB brains [35,36]. This may represent axonal transport defects and presynaptic dysfunctions [35,36]. Recent study showed that mutant αSyn (A53T) diminished levels of various motor proteins in neurons [37], supporting this scenario. Alternatively, excessive amount of misfolded αSyn and p-αSyn may aggregate at synapses, physically preventing the targeting of other presynaptic proteins [5]. In experiments using *Caenorhabditis elegans* overexpressing human αSyn, four genes related to the endocytosis process were identified as genetic modifiers for αSyn toxicity [38]. They included two subunits of the adaptor protein (AP) complex 2, which interacts with clathrin and promotes presynaptic clathrin-mediated vesicle recycling [39]. Furthermore, proteomics analysis revealed that p-αSyn also preferentially interacted with the proteins involved in endocytosis, including clathrin heavy chain and subunit of AP-2 and AP-1 complexes, over the non-phosphorylated αSyn [40]. Clathrin-mediated recycling of exocytosed synaptic vesicles occurs in the periaxial zone, a region adjacent to the active zone where synaptic vesicle is endocytosed [33]. Similarly, in *Snap25*^{S187A/S187A} mice, immunoelectron microscopy showed preferential localization of αSyn at the periaxial zone of excitatory presynaptic nerve terminals. This might reflect the interaction of αSyn and p-αSyn with the proteins involved in clathrin-mediated endocytosis. Taking these findings together, presynaptic accumulation of αSyn and p-αSyn could disturb the endocytosis process and consequently contribute to the development of VGLUT1-positive terminal enlargement [19].

Presynaptic accumulation of αSyn

Presynaptic accumulation of αSyn is considered an early event in the pathogenesis of α-synucleinopathies [4-6]. Mice overexpressing human αSyn showed presynaptic accumulation of αSyn and low DA release in the striatum. Stoica et al. [41] reported a “dying back” type of neuronal alteration, progressing from the dendrites to the axon and then to the perikaryon and nucleus in a spontaneously inherited autosomal recessive rat model for PD that overexpressed αSyn in mesencephalic area.

Transmission electron microscopy (TEM) examination revealed that the retrograde pathological process in substantia nigra and striatum starts at the synaptic level by marked presynaptic accumulation of α Syn followed by post-synaptic degeneration of axonal terminals, dendrites and spine alterative changes and perikaryal aggregation of mitochondria with relative preservation of neuronal nuclei. These findings were associated with abnormal distribution of SNARE proteins, which colocalized with α Syn aggregates. Similarly, accumulation of SNARE proteins and α Syn were reported in the striatum of PD patients [18]. These observations suggest that SNARE dysfunction likely occurs at an early stage of pathogenesis in nigrostriatal dysfunction observed in PD. Considering the findings observed in the VGLUT1-positive nerve terminals, we expected that SNARE dysfunction might have induced presynaptic accumulation of α Syn, which consequently result in the development of neurodegenerative changes in the nigrostriatal system. However, contrary to our expectation, *Snap25*^{S187A/S187A} mice showed no significant neurodegenerative changes in nigrostriatal dopaminergic neurons, suggesting that SNARE dysfunction alone was insufficient to cause nigrostriatal degeneration as observed in PD, and appeared to be a downstream event associated with abnormal accumulation of α Syn.

Conclusion

In conclusion, SNARE dysfunction leads to accumulation of endogenous α Syn in the corticostriatal nerve terminals. Presynaptic accumulation of α Syn is considered to be an early key event in the pathogenesis of α -synucleinopathies. Although the “prion-like” propagation hypothesis of α Syn, including tau and TAR DNA-binding protein 43 kDa, is currently receiving considerable attention worldwide, our findings provide an insight to understanding of the possible mechanisms that lead to presynaptic accumulation of endogenous α Syn. Moreover, given that SNAP-25 is reduced in the striatum of MSA brains [42], we speculate that a discontinuous pattern of α Syn pathologies usually found in MSA, *i.e.* glial cytoplasmic inclusions (GCIs) in the putaminal oligodendrocytes, and neuronal cytoplasmic inclusions (NCIs) and neuronal nuclear inclusions (NNIs) in the cortex [43,44], might be potentially linked through the presynaptic accumulation of α Syn in the corticostriatal neurons. Further investigations on the *Snap25* mutant mice with genetic ablation of α Syn would contribute to understanding the essential role of redistributed α Syn.

Competing interest

The authors have no conflict of interest.

Authors' contribution

TY, YN, and CJC wrote the paper. HM supervised the work. All authors read and approved the final manuscript.

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