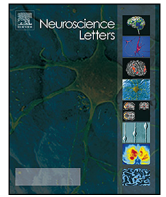
Neuroscience Letters 663 (2018) 66–71

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet



Review article

The PMR1 pump in alpha-synuclein toxicity and neurodegeneration

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HIGHLIGHTS

- PMR1, a Golgi resident pump, regulates calcium and manganese ion homeostasis.
- Neurons are highly dependent on proper PMR1 function.
- α-synuclein influences calcium signalling.
- Mn2+ and Ca2+ are likely modulators of α-synuclein toxicity.

ARTICLE INFO

Article history:
Received 3 July 2017
Received in revised form 26 July 2017
Accepted 1 August 2017
Available online 2 August 2017

Keywords:
Alpha-synuclein
ATPase
Caenorhabditis. elegans
Golgi
Ionostasis
Lewy bodies
Neurodegeneration
Parkinson's disease
PMR1
Proteinopathies

ABSTRACT

Proteinopathies constitute a diverse group of devastating neurodegenerative disorders, characterized by aberrant aggregation of specific proteins within neurons and in the brain parenchyma. Parkinson's disease (PD) is among the most common proteinopathies, caused by the accumulation of different species of α-synuclein and the formation of protein inclusions known as Lewy bodies. Although several mutations in the α-synuclein gene have been linked to PD, the mechanisms mediating the aggregation and toxicity of α-synuclein are not fully understood. Here, we review recent evidence that highlight an intricate interplay between α-synuclein and ionostasis, focusing on the PMR1 pump, a Golgi resident Ca^{2+}/Mn^{2+} P-type ATPase, which plays a pivotal role in regulating the intracellular levels of calcium and manganese ions.

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Contents

1. Introduction: ion homeostasis in neurons 67
2. The Golgi apparatus in neurons 67
3. α-Synuclein-induced neurotoxicity 68
4. The role of PMR1 in synuclein-mediated neurotoxicity 68
5. Manganese metabolism in neuronal health 69
6. Concluding remarks and open questions 69

Funding statement 70
Acknowledgements 70
References 70

Abbreviations: AAV, adeno-associated virus; CEDE, calcium-evoked dendritic exocytosis; ER, endoplasmic reticulum; MSA, multiple system atrophy; PMCA, plasma membrane Ca2+ ATPase; SERCA, sarco/ER Ca2+-transport ATPase; SNARE, SNAP receptor.

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https://doi.org/10.1016/j.neulet.2017.08.006
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1. Introduction: ion homeostasis in neurons

A transient fluctuation in the cytoplasmic concentration of calcium is the main second messenger for major processes facilitating neuronal function, including excitability, integration of electrical signals, synaptic plasticity, gene expression, metabolism and cell death, as reviewed elsewhere [43]. Therefore, ionostasis, the homeostasis of ionic concentrations, and particularly of calcium, is essential for neuronal integrity and its deregulation can lead to various pathological states. Selective triggering of these processes is achieved by spatially localizing calcium surges [5] by mechanisms residing not only on the plasma membrane, but also in intracellular organelles, providing additional layers of spatial and temporal control.

Along with their central role in post-translational modifications and sorting of secreted, membrane and lysosomal proteins, the organelles of the secretory pathway play a pivotal role in the regulation of ionostasis, most predominantly of calcium. It is well established that the smooth ER functions as the main internal calcium reservoir, sequestering intracellular calcium by the action of the Ca^{2+}-ATPase [56]. Activation of inositol triphosphate (IP3) receptors or ryanodine receptors triggers the release of calcium from the ER into the cytoplasm, facilitating a number of signalling pathways that underlie synaptic function.

Early work with calcium fluorescent indicators revealed that besides the ER, there is a region of high calcium content at the perinuclear area of cells, which in dividing cells is especially apparent during telophase, and was identified to be the Golgi apparatus [13,57]. Consistent with this early observation, the Golgi is known to undergo a reversible disassembly during mitosis.

Two types of calcium pumps lie in the heart of the function of the Golgi in ionostasis, the well characterized sarco/ER Ca2+-transport ATPases (SERCAs) and the less known PMR1 pumps. PMR1, also known as SPCA1, belongs to the family of P-type ion-motive ATPases [49], which is evolutionarily conserved from yeast to mammals [4]. PMR1 pumps are distinct from the (SERCAs), as well as from the Ca^{2+} pumps found on the plasma membrane (PMCA), but may be phylogenetically closer to the Ca^{2+} ATPases found in some bacteria such as *Bacillus subtilis* [46], suggesting that they may represent the most ancient class of Ca^{2+} pumps in eukaryotes.

Unlike SERCAs that are localized both in the ER and in the Golgi apparatus, PMR1 pumps are exclusively found in Golgi stacks of the *trans*-Golgi network and some secretory vesicles [4]. Another major difference is that while SERCAs translocate two Ca^{2+} ions, PMR1 pumps translocate only one ion per cycle. Consistent with this, of the two Ca^{2+} binding sites found in the transmembrane domain of SERCAs only one (site II) is conserved in PMR1, as well as in PMCA. Despite this high degree of conservation in the calcium binding site, PMR1 can catalyze the translocation of either Ca^{2+} or Mn^{2+} with the same efficiency, while SERCAs are specific for Ca^{2+} [12,21]. Finally, PMR1 pumps, similarly to PMCA, are not sensitive to SERCA inhibitors, such as thapsigargin.

Therefore, PMR1 pumps function to establish the correct ionic environment with respect to two ions, Ca^{2+} and Mn^{2+}, which is required for the function of pro-protein convertases and secretases mediating the maturation of secretory products. Their specific localization and characteristics add another layer of temporal and spatial complexity for calcium and manganese-mediated signalling that has been thus far overlooked. Consistently, any perturbation in PMR1 function should be examined in the light of the effects brought about by deregulated concentrations of both calcium and manganese inside the Golgi and in the cytoplasm.

As SERCAs and PMR1 are co-expressed in the Golgi, it is generally thought that their relative contribution to the Ca^{2+} uptake by the Golgi may be cell type-dependent. This is suggested by findings that keratinocytes are more dependent on PMR1 compared to COS7 cells. This observation is also in line with the fact that mutations in the *pmr-1* gene cause Hailey–Hailey disease in humans, which is characterized by keratinocyte dysfunction and chronic skin lesions. Therefore, removing calcium and manganese from the cytosol to intracellular stores is crucial for skin integrity and for the regeneration of skin cells after damage. This notion is also supported by a *C. elegans* model of the disease. In addition, analysis of *pmr-1* mutant *C. elegans* embryos revealed severe defects in cell migration and attachment for a population of cells tracked, including neuronal precursors [45].

2. The Golgi apparatus in neurons

Neurons are highly polarized cells, with one axon containing the machinery for releasing neurotransmitters and propagating action potentials, while dendrites, which can often assume very complex morphologies, contain the machinery that responds to neurotransmitter release. At most excitatory synapses in the CNS, presynaptic boutons directly appose to tiny dendritic protrusions called spines, harbouring post-synaptic densities. As these structures are often far away from the soma, synaptic proteins must either be trafficked over long distances or produced locally in the vicinity of synaptic activity.

Neurons have evolved elaborate adaptations of the core secretory machinery to cope with the challenges imposed to them by their complex shape and needs. In most eukaryotic cells the ER extends throughout the cell, while the Golgi network is confined near the nucleus and the microtubule organizing center [34]. In neurons, however, the Golgi apparatus appears continuous in the neuronal cell body and proximal dendrites [20,28]. Moreover, the realization that protein synthesis [19] and glycosylation [52] can occur locally in dendrites, as well as evidence for active ER exit sites throughout dendrites [28] inspired the search of dendritic Golgi. Protein markers for *cis*-, medial- and trans-Golgi labelled structures, in a subpopulation of dendrites, including dendritic segments that were far away from the soma. To address whether these Golgi protein-positive structures are functional Golgi apparatuses, ER to Golgi trafficking was monitored by live imaging in neurons, which captured the movement of fluorescently tagged proteins from the ER to these dendritic Golgi outposts. Therefore, though the somatic Golgi structure is similar to that of non-neuronal cell types, a more extensive, dispersed network of Golgi elements for protein processing is found in remote neuronal compartments, which were termed Golgi outposts. Although the mechanisms mediating the generation of the dendritic Golgi outposts remain unclear, recent work has revealed that increased neuronal activity fragments the Golgi complex to generate outposts [51].

The fact that many forms of long lasting synaptic modulation, such as long term potentiation and depression depend on postsynaptic Ca2+ signals also from intracellular calcium stores [22], raises the possibility that Golgi outposts resident at the synapse may act as local calcium stores. In line with this, recent work has revealed that local calcium release in dendritic spines is required for long term synaptic depression [41], as well as for rapid synaptic partner selection by dendritic filopodia [36]. In addition, calcium-evoked exocytosis, traditionally thought to be confined to presynaptic sites of neurons, has been shown to also occur on the post-synaptic side, known as calcium-evoked dendritic exocytosis (CEDE) [38]. Therefore, the organization of neuronal Golgi structure into dendritic outposts is likely to facilitate not only the rapid delivery of receptor and secreted proteins near synapses in responses to synaptic activity [29], but to also modulate all the calcium-evoked responses associated in its capacity as a calcium store. However, the contri-

bution of the Golgi and PMR1 to the local calcium homeostasis in dendrites remains unknown.

While there is no extensive study on the relative contribution of PMR1 in neuronal and dendritic calcium and manganese ionostasis, several lines of evidence indicate that neurons are highly dependent on proper PMR1 function. Part of this evidence arises primarily from the field of proteinopathies, where impaired homeostasis of both calcium and manganese has been demonstrated to have a crucial role in neurotoxicity.

3. α-Synuclein-induced neurotoxicity

Point mutations or multiplications in the *SNCA* gene encoding for α-synuclein, have been identified in patients with dominantly inherited forms of Parkinson's disease (PD) [27], while polymorphisms in the *SNCA* gene are associated with increased susceptibility to sporadic PD [42] and multiple system atrophy (MSA) [48]. Both in PD and MSA, insoluble and fibrillary α-synuclein is a major component of the protein inclusions (Lewy bodies). Additionally, α-synuclein was also identified as a component of amyloid from brain tissues of Alzheimer's disease (AD) patients [54]. Numerous studies in various model organisms have provided evidence for the importance of soluble oligomers as the prominent toxic species in synucleinopathies, although the precise size and type of the toxic oligomeric species remains to be determined [40].

α-synuclein is a 140 amino-acid protein that is highly expressed in the brain and was originally described to localize to the nucleus of neurons and to weakly associate with synaptic vesicles [39]. Its affinity for ionic membranes with high curvature has been demonstrated both *in vitro* and *in vivo,* as well as its interaction with membrane associated lipids and lipid rafts [40].

While α-synuclein is thought to modulate neurotransmitter release, its physiological roles have not been fully elucidated and its precise function remains disputable. Recently, the C-terminus of α-synuclein was found to directly bind the N-terminus of the SNARE protein synaptobrevin-2 and this interaction was shown to enhance the assembly of SNARE-complex both *in vitro* and *in vivo* [9]. However, another study suggested that α-synuclein inhibits SNARE-complex assembly by sequestering arachidonic acid [15]. Mice lacking α-synuclein exhibit functional deficits in the nigrostriatal dopamine system, displaying reduced striatal dopamine and altered dopamine release [1]. Another *in vivo* study showed that α-synuclein deficiency leads to a permanent increase of the vesicle refilling rate and thus in the dopamine readily releasable pool [58]. Analysis of alpha-, β- and γ-synuclein triple knockout mice have revealed that loss of synuclein function leads to an age-dependent impairment of SNARE-complex assembly and loss of neuronal function [23]. Very recent work demonstrated that α-synuclein promotes the dilation of the exocytotic fusion pore, thus accelerating the kinetics of individual exocytotic events by promoting cargo discharge and reducing pore closure ('kiss-and-run') [35]. Together, these findings suggest that α-synuclein is an activity-dependent modulator of dopamine neurotransmission, while it has also been shown to affect the synaptic release of glutamate [26,47].

4. The role of PMR1 in synuclein-mediated neurotoxicity

Modulation of endogenous cellular defence mechanisms via stress response pathways represents an innovative approach for novel therapeutic interventions in neurodegeneration. In this context, hormesis is receiving increasing attention, and PMR1 has been identified as a pivotal component of an evolutionarily conserved hormetic mechanism that protects neurons upon preconditioning.

Hormesis describes a process by which cells or organisms gain resistance to harmful insults by prior exposure to milder insults. In other words, pre-conditioning to a mild adverse stimulus sets the cellular machinery in motion for battling and prevailing upon forthcoming insults, securing cell survival and organismal fitness. Recent work has elucidated that PMR1 is fundamentally involved in neuronal hormesis against various harmful insults, as it is both necessary and sufficient to mediate the protective effects of preconditioning in a paradigm of heat stroke [32]. PMR1 acts together with the small heat-shock protein HSP-16.1 in the Golgi to maintain Ca^{2+} homeostasis and prevent a cytosolic Ca^{2+} overload under heat stroke that is typically associated with necrotic death. While this cyto-protective mechanism was first described in *C. elegans*, it was found to be evolutionarily conserved in murine neurons. Relevant to the field of neurodegeneration, PMR1-mediated preconditioning was efficient in alleviating not only heat-induced cell death but also neuronal demise inflicted by a variety of neurotoxic stimuli including in particular α-synuclein aggregation [32].

In line with these findings, α-synuclein was found to induce an increase in basal levels of intracellular calcium in its unfolded monomeric state as well as in its oligomeric state. Moreover, α-synuclein oligomer-induced cell death was abolished by the exclusion of extracellular calcium [3,14]. These findings confirm that α-synuclein interacts with membranes to affect calcium signalling in a structure-specific manner, ultimately leading to calcium dysregulation and calcium dependent cell death.

In contrast to the notion of PMR1 being cytoprotective against α-synuclein induced neurotoxicity by preventing the intracellular overload of calcium, recent work identified PMR1 as a phylogenetically conserved mediator of α-synuclein-driven cytotoxicity [10]. Expression of α-synuclein in yeast resulted in elevated cytosolic Ca^{2+} levels and increased cell death, both of which could be inhibited by deletion of PMR1. Consistently, absence of PMR1 prevented α-synuclein-induced loss of dopaminergic neurons in nematodes and flies [10]. Thus, the toxic consequences of α-synuclein expression in yeast, nematodes and flies essentially require PMR1. Taken together, these findings indicate that while a transient activation of PMR1, as in the case of preconditioning, mediates cytoprotection against α-synuclein by preventing a calcium overload in the cytosol, the permanent loss of PMR1 function caused by the genetic deletion of the gene may create a milieu that augments toxicity.

In addition to mediating or preventing the cytotoxic effects of α-synuclein, PMR1 activity may also be involved in the secretion of α-synuclein. The absence of a secretory signal peptide sequence in α-synuclein suggested it might be purely an intracellular protein and its pathological function was, therefore, studied in a cell autonomous context. However, this view has been challenged by the presence of α-synuclein in biological fluids of both PD and normal subjects [17] and by the detection of α-synuclein in the culture medium of cell lines overexpressing it. Most importantly, endogenous α-synuclein was also found to be secreted from rat embryonic cortical neurons [33].

The mechanisms of α-synuclein secretion are not fully understood. On the one hand, α-synuclein has been detected in dense core vesicles [35], known to mediate the release of many neuropeptides, while on the other, there is evidence showing that α-synuclein can be secreted by non-classical, ER/Golgi-independent protein export pathways [33]. A fraction of α-synuclein was shown to be secreted by exosomes in a calcium-dependent mechanism [18] and exosomal α-synuclein release was found to be increased upon lysosomal dysfunction [2]. Therefore, If the release of α-synuclein is mediated by calcium surges, it is conceivable that sequestration of cytosolic calcium by PMR1 may prevent its release, hence explaining the rescue of α-synuclein neurotoxicity by PMR1-mediated heat preconditioning or by chelation of calcium. However, this hypothesis needs to be experimentally tested in genetic mutants of PMR1 and using biochemical and other methods to reliably measure α-synuclein release from neurons.

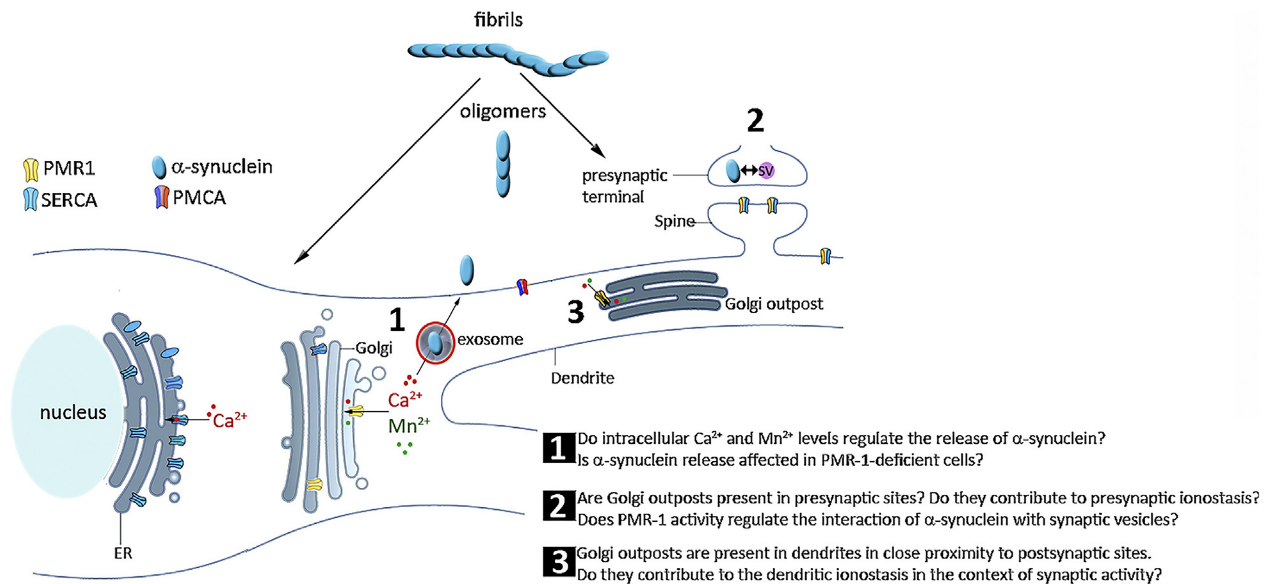

Fig. 1. Open questions on the role of PMR-1 in neurons and a-synuclein toxicity. Schematic representation of calcium pumps in distinct subcellular locations. SERCA pumps are present on the ER and Golgi, while PMR-1 is found only on the Golgi and the Golgi outposts in dendrites. Finally, the PMCA pump is localized to the plasma membrane. PMR-1 pump regulates the import of both calcium and manganese cations into the Golgi, preventing their accumulation in the cytoplasm. Three key topics that remain elusive are listed here: (1) The role of PMR-1 in the release of a-synuclein, (2) The role of Golgi outposts in presynaptic sites and (3) The contribution of Golgi outposts and PMR-1 in dendritic ionostasis.

While PMR1 has emerged as a hub for molecular pathways associated with α-synuclein toxicity [11], a very recent study undertook a systematic mapping of the molecular pathways underlying the toxicity of α-synuclein using new computational methodologies. This work has marginalized hub genes such as PMR1 and identified 332 genes that impact α-synuclein toxicity and are shared in various proteinopathies [30], and which were previously missed by conventional methods.

Although several studies have strongly suggested that impaired presynaptic function is the overall mechanism mediating α-synuclein-induced pathology, the effects of α-synuclein on the postsynaptic site and the possible role of endogenous α-synuclein in dendrites remains poorly investigated. Recent findings reveal that seeding and transgenic overexpression of α-synuclein trigger dendritic spine pathology in the neocortex, including in particular spine loss and dystrophic deformation of dendritic shafts in layer V pyramidal neurons [8]. These findings are in line with previous work indicating that AAV-mediated delivery of α-synuclein in the *substantia nigra* of adult marmosets caused severe defects in dendrites projecting into the *pars reticulata* [31]. Whether these defects are secondary to presynaptic defects, or if they are directly caused by impaired calcium homeostasis in dendrites remains to be elucidated. However, it is plausible that once secreted α-synuclein can alter membrane dynamics and increase intracellular calcium alongside the neuronal plasma membrane, including in dendritic compartments, the synaptic properties of which are highly sensitive to fluctuations in cytosolic calcium. As already mentioned, dendrites contain Golgi outposts that may also contribute to local ionostasis, hence the role of the Golgi and of PMR1 in dendrites in response to α-synuclein is a topic that needs further investigation.

5. Manganese metabolism in neuronal health

Unlike calcium, manganese is rather scarce in the human brain. Despite its low abundance, manganese has an important role in brain and muscle development, as it is a cofactor of several enzymes such as transferases, hydrolases and superoxide dismutase [25].

Manganese intake is mainly through dietary sources containing the metal in trace amounts. Exposure to excess amounts of Mn^{2+} either due to nutritional toxicity, or more often due to excess Mn^{2+} exposure in occupational settings, leads to Mn^{2+} poisoning known as "manganism," an irreversible, progressive condition that resembles Parkinson's disease (PD) and entails cognitive deficits [24,37]. Moreover, increasing evidence indicates that genetic mutations in genes involved in Mn^{2+} metabolism, such as the uptake transporter SLC39A14 [53], or the lysosomal P5-type cation-transporting ATPase ATP13A2 [50] cause parkinsonism.

The possible interplay between α-synuclein and Mn^{2+} has recently been a topic of intense investigation, extensively reviewed elsewhere [44]. Briefly, a bidirectional interaction is emerging, where on the one hand Mn^{2+} can influence the folding, uptake and intracellular accumulation of α-synuclein [6,55], while on the other, α-synuclein overexpression can also lead to increased intracellular concentration of Mn^{2+} [16]. Despite these findings, a direct binding of α-synuclein and Mn^{2+} has not been demonstrated and NMR studies show a poor affinity between the two [7].

Therefore, these findings suggest that Mn^{2+} as well as Ca^{2+} may act together, as common modulators of α-synuclein-induced toxicity. In this case, PMR1, which functions in importing Mn^{2+} cations from the cytosol into the Golgi, with equal affinity as it does for Ca^{2+}, thus dually affecting the ionostasis of both cations, may represent a promising target for novel therapeutic interventions.

6. Concluding remarks and open questions

Numerous recent studies have implicated PMR1 in the pathophysiology of neurodegenerative disorders, including multiple proteinopathies. Perturbation of PMR1 function in neurons severely impacts Mn^{2+} and Ca^{2+} homeostasis, as well as general ionostasis in neurons. In turn, compromised ion homeostasis degrades the capacity of neurons to cope with proteotoxic insults, including α-synuclein toxicity. While significant progress has been made towards deciphering the relevant mechanisms, many questions and gaps in our understanding of the involvement of PMR1 in neuronal physiology and neurotoxicity still remain (Fig. 1). An important issue is whether PMR1 is involved in the transport and release of endogenous α-synuclein in neurons. In addition is not

clear whether activation of PMR1 can be protective against the dendritic defects caused by α-synuclein toxicity. Finally, the role of PMR1 activity in normal dendritic plasticity needs to be further delineated. Elucidation of these aspects of PMR1 function will likely facilitate the development of intervention strategies aiming to ameliorate neurodegeneration.

Funding statement

This work was funded by grants from the European Research Council (ERC) and the European Commission 7th Framework Programme to V. N. and N. T..

Acknowledgements

We apologize to those colleagues whose work we could not reference directly owing to space limitations.

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