Minireview

α-Synuclein regulation of the dopaminergic transporter: a possible role in the pathogenesis of Parkinson's disease

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Received 27 January 2004; accepted 1 March 2004

First published online 9 April 2004

Edited by Jesus Avila

Abstract Parkinson's disease (PD) is a slow progressive neurodegenerative disorder. Recent evidence suggests a central role for α-synuclein, a protein of unknown function, in the genesis of PD. The phenomenon of selective degeneration of dopaminergic neurons in PD may be linked to the potential toxicity of dopamine itself and aberrations in the processes which regulate dopamine content may underlie the pathogenesis of this disease. Here, we review a vital role of α-synuclein in the modulation of dopamine transporter (DAT) function, and describe how disruption of this modulatory process permits increased re-uptake of high levels of intracellular dopamine by DAT, causing profound neurotoxicity.

Keywords: Dopamine transporter; α-Synuclein; Parkinson's disease; Synucleinopathies; 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyrimidine; Neurodegeneration; Lewy bodies

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disease, primarily affecting the elderly, characterized by a progressive impairment of automatic aspects of behaviors, namely sensory neglect, hypokinesia and rigidity. The pathological hallmarks of PD are a striking loss of dopamine-producing neurons in the substantia nigra (SN), causing dopamine depletion in the striatum, on the one hand, and the presence of neuronal cytoplasmic inclusions known as Lewy bodies (LBs), on the other hand [1]. Although oxidative stress and mitochondrial dysfunction have been implicated in the disease process, the mechanisms underlying the selective death of nigral neurons in PD are still unknown. Most cases of PD are sporadic, but rare, familial forms of the disease do exist. To date, early-onset PD has been linked to mutations in four genes, *α-synuclein*, *parkin*, *UCH-L1* and *DJ1* [2–4]. Autosomal dominant forms of the disease result from mutations in α-synuclein leading to Alanine[30]–Proline [A30P] and Alanine[53]–Threonine [A53T] substitutions [5,6]. Even though these mutations are not present in the majority of patients with familial PD [7], and not found in idiopathic PD [8], numerous studies showed the selective accumulation of α-synuclein in LBs [9,10], suggesting a central role for wild type (wt) α-synuclein in mediating dopamine (DA) neuronal death [11–14].

In this review, we will present evidence to show that one of the normal functions of α-synuclein is the modulation of dopamine transporter (DAT) function, regulating the synaptic tone of dopamine. Disruption of this function of α-synuclein can result in abnormal intracellular and extracellular dopamine content, which can ultimately lead to neurodegeneration of the nerve terminals. Moreover, through its regulation of the DAT, we present evidence to support our hypothesis of a contribution of α-synuclein to the highly selective degeneration of dopamine-producing, DAT expressing neurons seen in PD.

2. α-Synuclein

α-Synuclein, a 140-amino acid protein of ~19 kDa [11,15,16], was originally isolated from cholinergic vesicle preparations of the electric organ of the ray *Torpedo californica* [17], and later from amyloid plaques of Alzheimer's disease brains [18,19]. α-Synuclein belongs to a multi-gene family encoding structurally closely related proteins that are abundantly expressed in presynaptic terminals of various brain regions and include the α-, β- and γ-synucleins [12,15,16]. α-Synuclein exists either as a poorly structured protein in aqueous medium or as an α-helix-shaped protein, when associated to phospholipids or cellular membranes. The function of α-synuclein is still unknown, although several studies suggest that it plays an important role in synapse maturation and maintenance [15,16,20]. Its expression is developmentally regulated, redistributing from neuronal cell bodies to synaptic terminals during periods of neuronal differentiation [15,21] and it is up-regulated during periods of synaptic plasticity [22]. Depletion of α-synuclein in neurons is associated with decreased production of synaptic vesicles, probably through its

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Abbreviations: PD, Parkinson's disease; SN, substantia nigra; LB, Lewy body; wt, wild type; DAT, dopamine transporter; ROS, reactive oxygen species; NAC, non-amyloid component; CT, carboxy-terminal tail; MPP^+, 1-methyl-4-phenylpyridinium; VMAT2, vesicular monoamine transporter

0014-5793/$22.00 © 2004 Published by Elsevier B.V. on behalf of the Federation of European Biochemical Societies.
doi:10.1016/j.febslet.2004.03.063

interaction with phospholipase D, a key enzyme of the phospholipid pathway ([20], and references therein).

How α-synuclein may be implicated in the pathophysiological process of PD is far from obvious, but a prerequisite of α-synuclein neuropathy is its oligomerization into soluble protofibrils [23,24] followed by their coalescence into insoluble fibrils [10,24], composed of β-sheets and amyloid-like filaments [25,26], prior to their aggregation into insoluble fibrillar structures and inclusions, which then accumulate into LBs [14]. Several experimental conditions, including overexpression of the protein, presence of the A30P or A53T mutations, exposure to neurotoxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyrimidine (MPTP) or rotenone, and oxidative factors, induce or accelerate α-synuclein aggregation, through procedures that remain poorly understood [13,14,26–28]. Once aggregation is initiated, the bioavailability of α-synuclein is substantially diminished such that normal physiological functions regulated by this protein may be severely compromised, which in turn, could further exacerbate the initial cellular insult.

A puzzling aspect of α-synuclein-mediated cytotoxicity and LBs formation with regard to PD is the preferential and selective neurodegeneration of dopamine-producing neurons of the SN, particularly since it is ubiquitously expressed at high levels in virtually all brain regions, accounting for up to 0.1% of total brain protein [11,12]. Increasingly, the evidence suggests that the specific vulnerability of these neurons is linked to the cytotoxic potential of dopamine itself, mediated both through its auto-oxidation catalyzed by free transition metals (mostly free Fe^{2+}) [29] and its enzymatic deamination by monoamine oxidases to yield toxic DA metabolites and reactive oxygen species (ROS), such as superoxide and hydroxyl radicals [30] (Fig. 1). Thus, a failure to properly regulate the intracellular content of DA may cause abnormally high cytosolic levels of DA, leading to generation of cytotoxic DA metabolites and ROS, which in turn can promote oxidative stress, terminal degeneration, and eventually neuronal death [20].

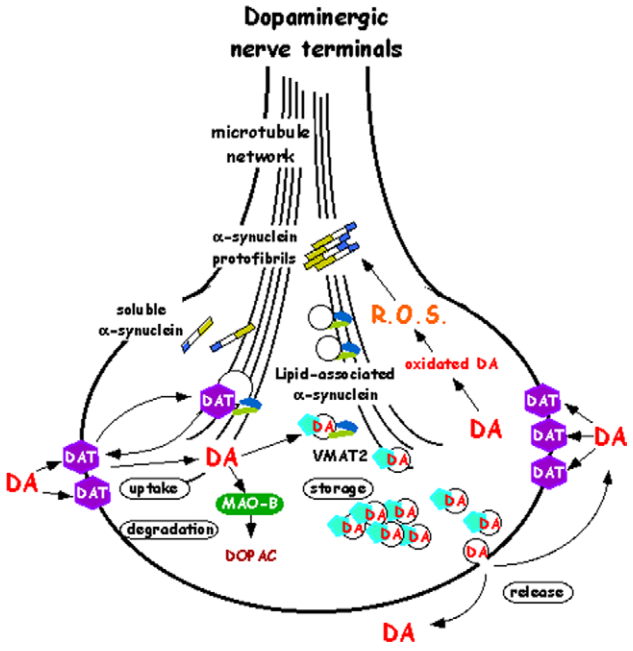

Fig. 1. The dopaminergic nerve terminals and the components that regulate dopamine metabolism at the nerve terminals. Synthesized DA (red) is accumulated and stored inside synaptic vesicles through the vesicular transporter VMAT2 (blue pentagons). After exocytotic release into the extracellular space, dopamine is fastly taken up by the plasma membrane DAT (violet hexagons), and then enzymatically degraded by monooxidase B (MAOB, green). The intracellular amount of free dopamine thus depends on the amount of DAT at the plasma membrane and on the availability of VMAT2 on synaptic vesicles. As soon as the amount of free dopamine increases inside the nerve terminals, oxidized dopamine and ROS (yellow) are produced and may be deleterious to the cells. The DAT shuttles between the plasma membrane and intracellular compartments, DAT endocytosis being favored by specific phosphorylation of the transporter and by the presence of α-synuclein. In normal situation, this latter exists either in soluble form or in membrane-bound form. Formation of protofibrils, upon either specific mutations (mainly A53T) or oxidative stress, tends to decrease the amount of soluble α-synuclein, to increase the amount of DAT at the plasma membrane and the amount of free dopamine in the neurons, triggering a vicious cycle of cellular stress.

3. α-Synuclein and its A30P mutant modulate the functional activity of the dopamine transporter

One of the main consequences of the presence of α-synuclein at the nerve terminals of dopamine-synthesizing neurons is its effects on the regulation of the plasma membrane DAT. As α-synuclein, the DAT is expressed in presynaptic terminals of SN dopaminergic neurons where it mediates the re-uptake of synaptically released dopamine ([31–33] and references therein) The importance of DAT function in the control of synaptic availability of dopamine suggests that its own regulation may be a crucial component in the maintenance of dopaminergic neurotransmission, and thereby in the levels of intracellular dopamine, since enhanced DAT activity would increase intracellular levels of dopamine, resulting in excessive ROS production within dopaminergic neurons (Fig. 1). DAT function is mostly regulated through its rapid shuttling to and from the plasma membrane [32]. A rapid redistribution and internalization of DAT occurs after its phosphorylation by various kinases [34–36], suggesting rapid adaptation of the neuron, in response to signal transduction-induced changes, to modulate DAT function.

We have recently shown that upon co-expression in L*tk*$^-$ fibroblasts, or in basal conditions in mesencephalic neurons, wt α-synuclein tends to markedly decrease (by 30–50%) DAT-mediated uptake of extracellular dopamine [37,38], at amounts of the two proteins that mimic the endogenous situation seen in normal rat SN [39]. The reduction in DAT activity was due to decrease in dopamine uptake velocity, without any changes in affinity or DAT expression levels. As a consequence, dopamine-induced oxidative stress and cytotoxicity were decreased in cells co-expressing DAT and wt α-synuclein. In the presence of wt α-synuclein, DAT was dynamically trafficked away from the plasma membrane into the cytoplasm, as indexed by reduced DAT presence at the plasma membrane by biotinylation experiments [38,40] (Fig. 1). From co-immunoprecipitation studies, α-synuclein was found to interact directly with the DAT, forming a protein:protein heteromeric complex in transfected cells, primary cultures of mesencephalic neurons and rat SN [37,38,41]. These interactions occurred between the non-amyloid component (NAC) domain (residues 58–107) of wt α-synuclein and the last 22 amino acids of the carboxy-terminal (CT) tail of DAT [38].

Similar to the wt α-synuclein, the A30P mutant also attenuated DAT function, trafficking DAT away from the plasma membrane and participating in the formation of protein:

protein complexes, again through the NAC domain (residues 58–107) of A30P and the last 22 amino acids of the CT tail of DAT [42]. Interestingly, the A53T mutant was unable to modulate DAT function and subsequent studies showed that this protein only very weakly interacted with the transporter [42].

Recent evidence from our laboratories suggests that cell adhesion may play a role in dictating the functional outcome of DAT/α-synuclein interactions. Thus, batch-transfection of co-transfected cells followed by cell detachment and reseeding using trypsin, resulted in the opposite effect of wt α-synuclein on DAT, i.e., an increase of DAT activity [38], in agreement with Lee et al. [41]. Moreover, mild trypsinization of co-transfected cells or of neurons, under conditions which do not cause a significant cell dissociation, reversed the attenuation of DAT function by α-synuclein [40] (Fig. 2). This effect of trypsin was mimicked by other proteases used to dissociate cells, such as collagenase or dispase, but not by proteases which do not significantly affect cell adhesion, such as chymotrypsin, pronase or papain [40]. Impaired cell adhesion did not disrupt the physical interactions between wt α-synuclein and DAT, but promoted a pronounced redistribution of the DAT, which is recruited at the plasma membrane [40] (Fig. 2), indicating that α-synuclein may act to tether the DAT to a cytoplasmic compartment, thereby keeping it away from the cell surface (Fig. 2). Similar effects were also seen with the A30P mutant, but not with the A53T variant.

Most interesting, however, was the finding that the parkinsonian syndrome-inducing agent, 1-methyl-4-phenylpyridinium ion (MPP^+), whose intracellular transport within neurons occurs specifically only through the DAT, also reversed the inhibitory effects of wt α-synuclein on DAT [38]. Under all experimental conditions, where the dopamine transporter activity was dysregulated, there was increased re-uptake of dopamine and dopamine-induced neurotoxicity, suggesting that disruption of the ability of wt α-synuclein to regulate DAT function may be one of the most important determinants in the genesis of dopaminergic neurodegeneration (Fig. 2).

4. α-Synuclein and its A53T mutant modulate the amount of the vesicular transporter vesicular monoamine transporter in dopamine nerve terminals

A striking aspect of our studies is the absence of any modulation by the A53T mutant of α-synuclein on DAT function. However, recent studies [20,43] suggest that the A53T mutant can modulate the vesicular monoamine transporter (VMAT2) [44]. In MESC2.10 human mesencephalic cells the presence of the A53T mutant decreased expression of VMAT2, accompanied by decreased potassium-induced, and increased amphetamine-induced, dopamine release [43]. The consequence of such increased levels of cytosolic dopamine was enhanced superoxide production and cytotoxicity [43]. These results suggest that the A53T mutant, through its effects on VMAT2, causes an impairment in vesicular dopamine storage and release. Although the mechanisms of α-synuclein depletion of VMAT2 are not known, it is probable that the decrease in the number of synaptic vesicles that accompanies impaired α-synuclein functions plays a role in this decreased amount of VMAT2 at the synapses.

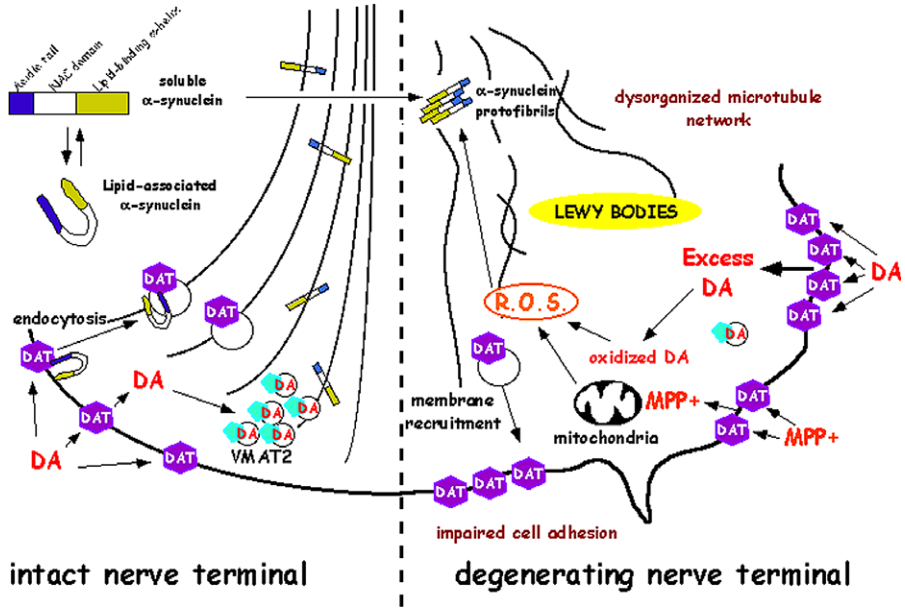

Fig. 2. The regulation of dopamine uptake in normal (left) and impaired (right) nerve terminals. In healthy nerve terminals (left part of the figure), the presence of sufficient amounts of soluble α-synuclein tends to decrease the amount of DAT at the plasma membrane. Thus, reasonable amounts of free dopamine enter the terminals, which are efficiently accumulated in synaptic vesicles through VMAT2 activity. As soon as cell adhesion or cytoskeleton integrity is impaired (or both, right part of the figure), α-synuclein is no longer able to favor the intracellular accumulation of DAT, which thus goes preferentially to the plasma membrane. Similarly, α-synuclein aggregation in fibrils or LBs tends to decrease the amount of soluble α-synuclein and triggers DAT recruitment to the plasma membrane. In this condition, dopamine is able to enter massively into nerve terminals and to form oxidized and reactive species. DAT is also the mean used by the mitochondrial poison MPP^+ to enter into neurons, triggering huge production of reactive, highly toxic oxygen species. Since oxidative stress strikingly favors α-synuclein aggregation and thus favors the presence of high amounts of DAT at the plasma membrane, a very efficient cascade of events takes place to trigger neuronal toxicity and degeneration. Clearly, the combined presence of α-synuclein and DAT in dopaminergic nerve terminals is a key-element to understand the specific degeneration of mesencephalic dopamine neurons in PD.

These findings, coupled with our own, suggest that all three variants of α-synuclein can regulate the function of the two key proteins that control the amount of dopamine inside nerve terminals, DAT and VMAT2. Thus, the wt α-synuclein and its A30P mutant can regulate the DAT, thereby controlling the extravesicular cytoplasmic levels of dopamine, while the A53T mutant regulates VMAT2, controlling the vesicular uptake of dopamine. Aberrations in any of these systems could cause increases in free cytoplasmic dopamine, which upon autoxidation and enzymatic metabolization can generate ROS, ultimately leading to neuronal death.

5. Dopamine-linked aberrations convert α-synuclein into a toxic molecule

In a normal situation, α-synuclein exists as a soluble or lipid-bound structure. In pathological states, α-synuclein can form protofibrils, reducing the bioavailability of the physiological form of the protein [24], and increasing the toxic potential of dopamine at nerves terminals (Fig. 2). Free radicals such as free iron or iron-centered radicals [29] and oxidized dopamine and catecholamines structurally related to dopamine [23], accelerate and stabilize the formation of α-synuclein protofibrils by inhibiting the conversion of toxic soluble protofibrils into insoluble fibrils. The formation of α-synuclein protofibrils is also facilitated by high levels of α-synuclein in vitro [27] and in transgenic *Drosophila* [45], or by the presence of the A53T mutation in mice [46]. Thus, it is clear that impaired storage of dopamine into synaptic vesicles, or dysregulation of DAT, will increase the levels of free intracellular dopamine, triggering a vicious circle of events, leading to aggregation of α-synuclein, thereby significantly contributing to the rather specific degeneration of the dopamine-synthesizing neurons of the mesencephalon in human PD. The lower amount of α-synuclein immunoreactivity observed by us in the SN, compared to other brain areas, suggests that nigral dopaminergic neurons may be particularly vulnerable to a pathological increase in α-synuclein protein levels [39].

Studies linking MPP^+ and α-synuclein effects further highlight the central role of the determinants of dopaminergic systems in the induction of the processes leading to α-synuclein toxicity (Fig. 2). Here, the expression of DAT confers the selectivity of MPP^+ toward SN [47], since this neurotoxin enters the dopaminergic neuron through DAT in an energy-dependent manner. Once in the cell, MPP^+ inhibits complex I of the mitochondrial respiratory chain, releasing cytochrome *c*, which accelerates aggregation of α-synuclein [48], ultimately affecting the properties of α-synuclein (Fig. 2). The presence of α-synuclein and its A53T mutant enhances the vulnerability of cells to MPP^+ exposure [49], whereas α-synuclein null-mice are essentially resistant to MPTP-induced degeneration of dopaminergic neurons [50]. This further suggests that α-synuclein has a facilitatory role in enhancing, either directly or indirectly, the observed toxicity of MPP^+.

6. Conclusion

To conclude, there is ample evidence to propose that overall, α-synuclein itself is not a toxic protein, but it can be converted to a toxic molecule in the presence of oxidized dopamine. In addition, α-synuclein regulates the major factors that regulate amounts of free dopamine in the dopaminergic neurons, DAT and VMAT2, thereby conferring the selectivity for degeneration of dopamine-producing neurons seen in PD. This hypothesis certainly does not recapitulate all the possible mechanisms envisaged to exist at the onset of PD, but it has the merit to include other well-demonstrated components of PD etiology, including genetic components and neurotoxins, which may all enter, at multiple entry points, into the deleterious cycle of α-synuclein protein aggregation and ROS production. Considering that DAT, VMAT2 and α-synuclein as key players in the chain of events leading to PD pave the way for therapeutic interventions, while providing a more accurate understanding of both the physiology and the pathology of dopamine neurotransmission.

Acknowledgements: Supported in part by grants from the National Institutes of Health [NS-34914 and NS-45326].

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