Alpha-synuclein and beta-amyloid - different targets, same players: calcium, free radicals and mitochondria in the mechanism of neurodegeneration

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Abstract

Two of the most devastating neurodegenerative diseases are consequences out of misfolding and aggregation of key proteins-alpha synuclein and beta-amyloid. Although the primary targets for the two proteins are different, they both share a common mechanism that involves formation of pore-like structure on the plasma membrane, consequent dysregulation of calcium homeostasis, mitochondrial dysfunction and oxidative damage. The combined effect of all this factors ultimately leads to neuronal cell death. Whereas beta amyloid acts on the astrocytic plasma membrane, exhibiting a tight dependence to the membrane cholesterol content, alpha–synuclein does not distinguish between type of membrane or cell. Additionally, oligomeric forms of both proteins produce reactive oxygen species through different mechanisms: beta-amyloid through activation of the NADPH oxidase and alpha-synuclein through non-enzymatic way. Finally, both peptides in oligomeric form induce mitochondrial depolarisation through calcium overload and free radical production that ultimately lead to opening of the mitochondrial permeability transition pore and trigger cell death.

INTRODUCTION

Neurodegenerative diseases are devastating and currently incurable, and are increasing progressively in aging populations. Neurodegenerative disorders, from most common Alzheimer's disease to prion disease are share a several common feature such an aggregation and deposition of misfolded proteins in the brain and involvement of calcium deregulation, energy disbalance and oxidative stress in pathogenesis. The most intensively studied misfolded proteins are beta-amyloid (main component of the extracellular senile plaques in Alzheimer's disease) and alpha-synuclein (aggregates as intracellular Lewy bodies in Parkinson's disease). These deposits consist predominantly of protein fibrils and have long been thought to be the trigger of cellular dysregulations and reason for neuronal loss in these diseases but in last several years the number of

studies proves that oligomeric forms of these proteins are more toxic than monomeric or fibril forms.

The role of unfolded proteins in neurodegeneration is intensively debating for number of years. As one of the argument is induction of neuronal loss before appearance of aggregated peptides and also localisation of the aggregated proteins – intracellular (for tau and α-synuclein) and β-amyloid (extracellular) with no trafficking through membranes. However, more toxic forms - oligomers are membrane permeable, allowing the passing of plasma and intracellular membranes and therefore protein propagation throughout neurons and astrocytes in the brain [41];[66]. The propagation hypothesis in neurodegenerative disease has found support when oligomeric forms of α-synuclein and tau have been found in cerebrospinal fluid and in neuronal graft studies. It also important that familial forms of AD are caused by a mutation in one of 3 genes which regulates βA production: presenilin 1 (PS1), presenilin 2 (PS2) and amyloid precursor protein (APP), that also prove importance of the β-amyloid studies. The role of aggregated α-synuclein in PD is also proven in familial (mutation in gene coding α-synuclein) and sporadic form of disease [63].

Calcium is the most pleiotropic ion and is able to trigger majority of intracellular pathways in all cell types in response to external or internal stimuli. In brain, and especially in neurons, Ca^{2+} plays a fundamental role in synaptic transmission, plasticity, transport, and neuron-neuron and neuron-glia signalling [22]. Any alterations of the physiological calcium signal in neurons or astrocytes lead to changes in signal transduction and cells death. Calcium dysregulation is shown to be one of the factors which trigger neurodegeneration in AD and PD [35;19].

There are a number of hypotheses concerning the pathogenesis of neurodegeneration in AD and PD, and these include the misfolding of proteins or the involvement of other pathological processes such as neuroinflammation or vascular pathology. Despite these different hypotheses for the aetiology of neurodegeneration, the unifying and undisputed feature seen in sporadic AD and PD is the occurrence of oxidative stress [36; 39].

Calcium signalling and enzymatic generation of reactive oxygen species are in close interaction and can stimulate each over in physiology [31;11;71]. The combined effect of oxidative stress and calcium deregulation is the trigger for cell death in the brain via multiple pathways [36;20]. Considering this, it is very important to shed more light on the nature of interplay between calcium signal and free radicals in the context of

perturbation of physiological conditions, mitochondrial dysfunction and neurodegeneration upon application of oligomeric misfolded proteins. Here we review the changes in redox state and calcium signalling in pathological conditions under the influence of misfolded proteins involved in two most common neurodegenerative disorders AD and PD.

Unfolded proteins and calcium signalling

β-amyloid

The possible role of the βA in pathological calcium signalling was discussed after finding the ability of βA 1-42 and 1-40 to form channels and pores in artificial membranes [14;15]. The effects of the βA on calcium signals were tested on the different cell types with broad variability of results [10]. One of the explanation of the diversity of the effects could be the fact that βA should be aggregated (oligomeric of fibril) for forming the pore in membranes and induce the calcium signal [28;29;43]. The effects of βA on the calcium signal are also cell specific. Thus, we have found that full peptides βA 1-42 and βA1-40 and different short forms βA 25-35, βA 25-40 or βA 1-28 in micromolar concentrations are able to induce $[Ca^{2+}]_c$ changes in astrocytes, but not in neurons [3;4;5;42]. Cytosolic Ca^{2+} elevation in astrocytes was crucial for neuronal cell death under βA exposure [3;7]. Importantly, the specificity of the βA to the astrocytes was not linked to any receptors or ion channels activation but was induced by incorporation of βA into the membrane with pore formation. This selectivity of the astrocytes to βA induced calcium signal is explained by their higher content of cholesterol in their plasma membrane compare to neurons [8]. Manipulation of the membrane cholesterol content in co-culture of neurons and astrocytes changes their ability to induce the calcium signal in response to βA and increase of cholesterol content in neuronal membrane make these cells to be able generate calcium signal in response to βA, while decrease of cholesterol in membranes block βA-induced calcium signal and neurotoxicity [8]. Importance of cholesterol for incorporation of βA into membrane and pore formation is shown by number of studies [30;53] and βA-induced channels can be blocked by compound, which compete with cholesterol for binding with C–terminal of βA [34]. βA is able to form pores on the plasma membrane of astrocytes (but not in neurons) in very low concentrations and only 1 molecules of oligomeric βA 1-42 can stimulate Ca^{2+}-influx to astrocyte [56].

α-synuclein

Oligomeric α-synuclein is also able to form pore-like structures with non-selective leakage of compounds [73;61]. Monomers of α-synuclein have also been reported to affect membranes

through differing mechanisms that is, altering permeability or inducing channel formation [72;74]. Interestingly, the effects of exogenous α-synuclein on the calcium signalling was in contrast to βA independent of cell type and it was able to induce elevation of cytosolic Ca^{2+} in both neurons and astrocytes from different brain regions [13]. Interestingly, monomeric α-synuclein, which play physiological role in synaptic transduction [21], also induced calcium signal in neurons and astrocytes in concentrations, which is close to physiological [13]. Both – monomeric and oligomeric α-synucleins are induced calcium signal, but only oligomers induced neuronal cell death, which can be prevented by inhibition of this signal by calcium free medium [13]. It suggests the importance of the calcium signal in neurodegeneration induced by aggregated βA and α-synuclein but strongly suggests some other coherent players in the mechanism of the neurodegeneration.

β-amyloid and α-synuclein induce ROS production via different mechanisms

The role of oxidative stress is increasingly recognised in neurological and neurodegenerative disorders [36;39]. Oxidative stress is caused by an imbalance in the redox state of the cell, either by overproduction of reactive oxygen species (ROS), or by dysfunction of the endogenous antioxidant systems. Increased levels of malondialdehyde and 4-hydroxynonenal (markers for oxidative stress – products of lipid peroxidation) were found in brain tissue and cerebrospinal fluid (SCF) of AD patients compared to controls [48]. This effect may be induced by βA, which able to accelerate lipid peroxidation in neurons and astrocytes [10].

Major antioxidant in the brain is glutathione (GSH). The level of GSH is the indicator of redox balance in the brain cells. We found that βA can induce profound decrease in glutathione of astrocytes. This effect could be averted in both neurons and astrocytes by inhibition of the astrocytic calcium signal using Ca^{2+}-free medium [3;4;5]. It suggests that βA induced calcium dependent ROS production in astrocytes which consequently affects neurons [6].

Oligomeric but not fibril or monomeric α-synuclein is able to induce oxidative stress that results in decreased level of GSH in neurons and astrocytes. Importantly triplication of α-synuclein also demonstrated reduction in glutathione in human neurons derived from iPS cells [26]. However, α-synuclein can directly activate glutathione peroxidase for prevention of oxidative stress [46].

βA produced ROS from the various enzymatic sources [57]. For oligomeric and fibrillar βA was also suggested production of free radicals in the interaction with copper [27]. βA can activate NADPH oxidase through several mechanisms, thus in neutrophils from Alzheimer's disease patients it can be stimulated through activation of P2X receptors, in microglia – through activation of the scavenger receptors CD36 [25]. We have found that full peptides βA 1-42 and 1-40 and also short peptides can activate astrocytic NADPH oxidase [4;6] after stimulation of

calcium signal, more likely through the Ca^{2+}-dependent activation of protein kinase C β [4;6]. Although expression of different forms of NADPH oxidase was also reported for neurons [18], βA did not activate ROS production in neurons, that can be explained by the absence of the βA – induced calcium signal [3;5]. Activation of NADPH oxidase in astrocytes is one of the key elements in the mechanism of βA-induced neurotoxicity – application of inhibitors of this enzyme is protective against neuronal and astrocytic cell death [4;6;16;40;58].

It is of particular importance that the βA-induced calcium signal is a trigger for NADPH oxidase activation. For example, inhibitors of NADPH oxidase, melatonin or antibodies for acetylcholine receptors failed to alter $[Ca^{2+}]_c$ in astrocytes but significantly reduced ROS production and protected both neurons and astrocytes against cell death [4;6;36;42;44]. Importantly, increased expression of Nox2 and Nox4 is shown for Alzheimer's brain and for cell cultures treated with βA.

α-synuclein

The ability of alpha-synuclein to produce ROS when externally added is directly dependent on its tertiary structure. In our hands only β-sheet-rich oligomers and to some extend fibrils of α-synuclein were able to produce significant rise in ROS production and to reduce the endogenous GSH levels [26]. We have shown that in cells with α-synuclein triplication as well as in primary neurons and astrocytes the rate of superoxide production, hydrogen peroxide production or generally lipid peroxidation are immensely augmented following application of nanomolar concentration of beta-sheet type oligomeric α-synuclein aggregates [12;26].

It has been largely speculated that alpha-synuclein could produce ROS through activation of the NADPH oxidase similar to β-amyloid (36). However, inhibitors of the NADPH oxidase such as 4-(2-aminoethyl)benzenesulfonyl fluoride (AEBSF) or dibenziodolium chloride (DPI), has been shown to be only partially protective against oligomeric α-synuclein-induced ROS [26]. These inhibitors are not highly specific to NADPH oxidase and influence the production of ROS by other cellular sources like NOS, XO or mitochondrial enzymes. Therefore the effect of α-synuclein on the activation of ROS production by NADPH oxidase is only secondary, most likely by increasing the permeability of the plasma membrane for calcium ions [13].

We demonstrated the increased of the basal ROS production rate in overexpression of α-synuclein in human iPSC model. Moreover, picomolar concentrations of externally applied beta-sheet form of α-synuclein oligomers produced excessive free radical productions that we found to be dependent on the presence of transition metals [26]. Thus, pre-treatment of the cells with metal chelators as desferrioxamine (DFO), clioquinol (CLQ), D-pencillamine (D-PEN), etc. to target iron, copper or zinc ions as potentially important in the ROS production be α-synuclein oligomers turned out to be largely protective [26].

Effect of misfolded proteins on mitochondria

β-amyloid

Despite the number of publications about localisation of the βA in mitochondria [9;52], effect of oligomeric and fibrillar peptide on the function of this organelle is more likely to be via βA-induced signals such a NO production, ROS generation and calcium signal [1;10]. βA induced two types of mitochondrial depolarisation in astrocytes – one, fast and transient, is calcium dependent, second type is slow and progressive and is dependent on the superoxide production from NADPH oxidase [4]. Importantly, chemical or molecular (gp91 kd) inhibition of NADPH oxidase protected astrocytes and neurons by blocking both types of mitochondrial depolarisation [6]. NADPH oxidase and calcium activate phospholipase A which participates in βA-induced mitochondrial depolarisation [75]. Combination of free radicals production and calcium overload induce opening of mitochondrial permeability transition pore (mPTP), which was a reason for fast and transient mitochondrial depolarisation [4;6;2] and cytochrome C release [45]. The effect of βA to induce PTP opening was proven on isolated mitochondria [59;68;54] and live cells [4;7]. Importantly, cyclophylin D knockout mice (model, which prevents or delay PTP opening) protects mitochondrial and neuronal disbalance and improve memory in Alzheimer's disease mouse model [32;33]. βA-induced slow mitochondrial depolarisation, which induced by inhibition of mitochondrial respiration by lack of substrates [2;23]. This effect is initiated by production of superoxide in NADPH oxidase, which damages DNA and activates DNA repairing enzyme PARP. PARP consumes NAD and limits NADH pool for mitochondrial respiration [2;70]. The activation of PARP is shown for patient's brain [24;47;60] Thus, βA-induced calcium signal activates free radicals production by NADPH oxidase, stimulates PARP activation and reduction of GSH that lead to mitochondrial deregulation, opening PTP and initiation of the cell death (Figure 1).

α -synuclein

Implication of mitochondria in pathology of Parkinson' Disease shown for long time, first for toxic models (rotenone and $MPTP^+$), complex I deficiency [65;69] and, more recently on familial form of this disease [20;37]. Oligomeric α-synuclein shown to be able to inhibit mitochondrial complex I [49;62] and induced mitochondrial depolarisation [17;67]. Importantly, cells with triplication of alpha-synuclein also demonstrated mitochondrial dysfunction [50;64]. The role of α-synuclein in mitophagy, mitochondrial fission/fusion and protein trafficking to this organelle is also shown [38;55]. α-synuclein transgenic mice is thought to induce neurodegeneration via activation of mitochondrial permeability transition pore [51]. Activation of mPTP opening by oligomeric α-synuclein seems more likely compared to monomeric peptide due to ability to induce calcium signal [13] and produce ROS in combination with heavy metal ions [26]– Figure 2.

Despite the high toxicity of βA and α-synuclein, the mechanisms of neurodegeneration induced by these peptides are very complex and could be prevented on different stages. One of the most important steps is oligomerisation of these peptides. Intercommunication of the cells, especially in βA toxicity, is also very important and neurodegeneration can be induced by activation of microglia or astrocytes [10]. Inside of the cells, activation of one process, such a calcium signal by oligomeric α-syn or βA activates enzymatic ROS production and combination of oxidative stress and calcium overload affect mitochondria which trigger the cell death cascade (Figure 1-2).

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Figure Legends

Figure 1. Interplay of calcium, oxidative stress and mitochondria in the mechanism of β-amyloid-induced neuronal cell death

Figure 2. The effect of α-synuclein on neurons. Both monomeric and oligomeric forms of α-synuclein modify plasma membrane and induce Ca^{2+} signal. Monomeric α-synuclein is not toxic for neurons despite inhibition of active calcium transport in neurons. Oligomeric α-synuclein producing free radicals and in combination with high calcium induce cell death.