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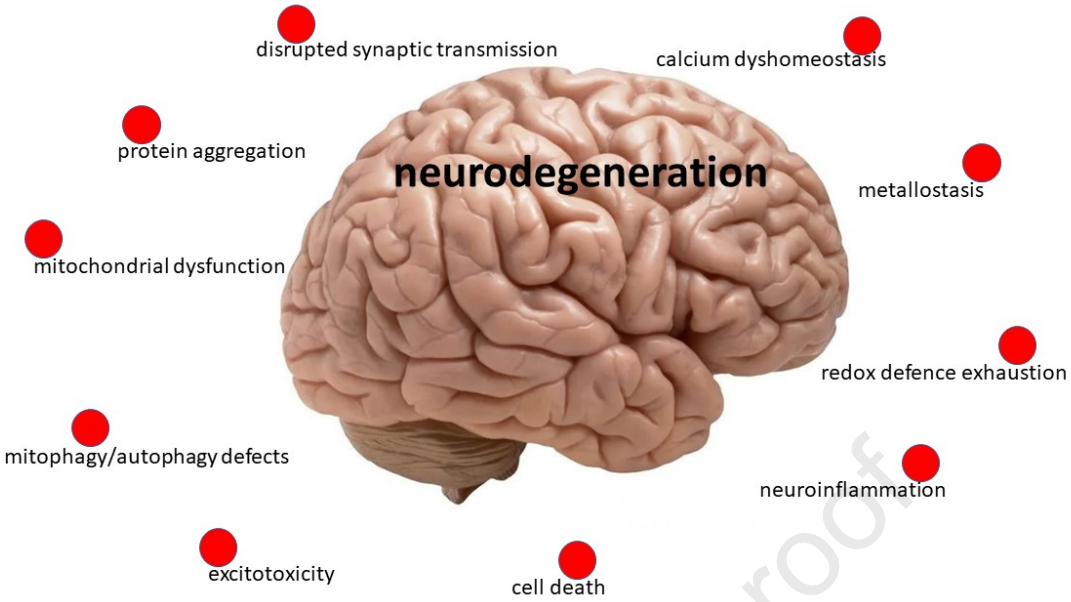

Sources and triggers of oxidative damage in neurodegeneration

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Highlights

- Misfolded and aggregated proteins in neurodegenerative diseases increase mitochondrial and cytosolic ROS production in neurons
- Transition metal dyshomeostasis leads to an increased ROS generation, ferroptosis and neurodegeneration
- Strong reduction in the function of redox defence systems in brain cells leads to oxidative stress and neurodegeneration

Abstract

Neurodegeneration describes a group of more than 300 neurological diseases, characterised by neuronal loss and intra- or extracellular protein depositions, as key neuropathological features. Multiple factors play role in the pathogenesis of these group of disorders: mitochondrial dysfunction, membrane damage, calcium dyshomeostasis, metallostasis, defect clearance and renewal mechanisms, to name a few. All these factors, without exceptions, have in common the involvement of immensely increased generation of free radicals and occurrence of oxidative stress, and as a result - exhaustion of the scavenging potency of the cellular redox defence [1] mechanisms. Besides genetic predisposition and environmental exposure to toxins, the main risk factor for developing neurodegeneration is age. And although the "Free radical theory of ageing" was declared dead, it is undisputable that accumulation of damage occurs with age, especially in systems that are regulated by free radical

messengers and those that oppose oxidative stress, protein oxidation and the accuracy in protein synthesis and degradation machinery has difficulties to be maintained.

This brief review provides a comprehensive summary on the main sources of free radical damage, occurring in the setting of neurodegeneration.

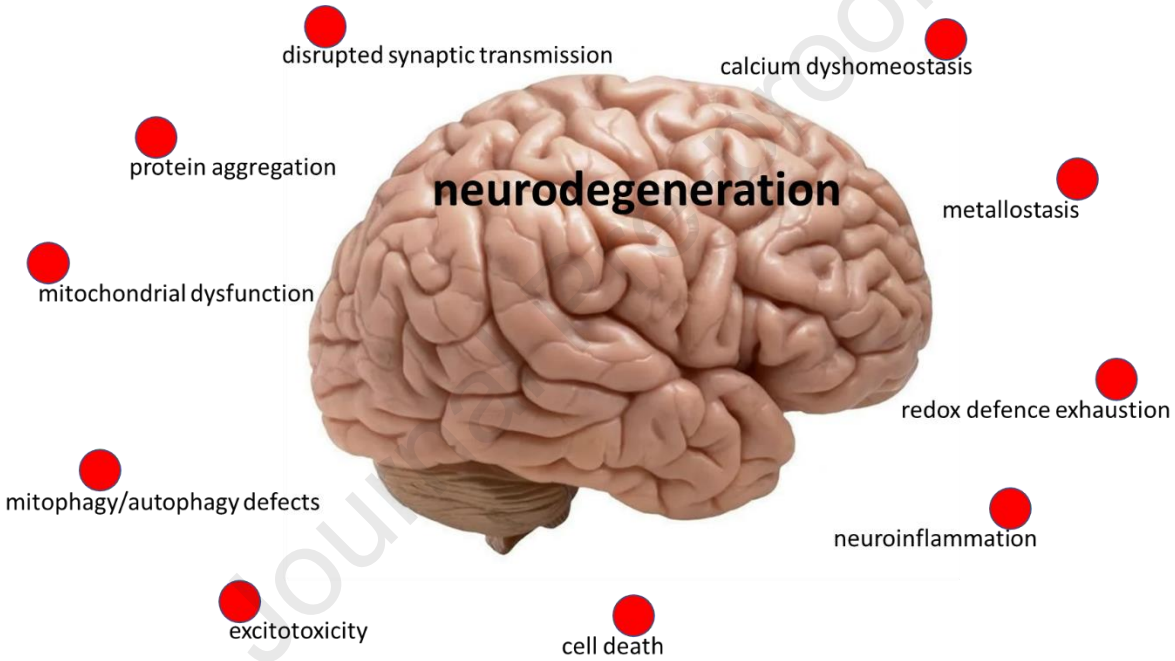
1.Introduction

The term “neurodegenerative diseases” represents a large group of various diseases of the nervous system with heterogenous clinical manifestation and diverse histopathological presentation. While the mechanism, despite many technology breakthroughs in the recent decades, is still largely unknown, neurodegenerative diseases have one in common: a progressive loss of neuronal structure and function, resulting in loss of neuronal viability. Despite that etiopathology of neurodegenerative diseases is still not well understood, there is sufficient body of literature that confirms the implication of multiple factors and therefore neurodegenerative diseases are accepted to be “multifactorial “disorders. Among others it is almost always the case when the following are observed histopathologicaly: altered protein folding and formation of insoluble aggregates, mitochondrial dysfunction, calcium dyshomeostasis, oxidative stress, transition metal accumulation, organelle quality control and protein degradation defects, neuroinflammation, and as a result of all these defects: neuronal cell death.

The relative short lifetime and the tight coupling to metabolic processes renders ROS/RNS, as well as the low levels of lipid peroxidation, well-fitted to exert various physiological signalling functions in the cell [1]. Thus, the dysbalance in production

/scavenging of ROS/RNS would represent not only oxidative stress *per se*, but also the disruption of physiological signalling to add another facete to the multifactorial face of ND.

The raison d'être of this review is to elucidate the interlinking role of ROS to the etiopathology of neurodegeneration, connecting the processes of lipid peroxidation, metal dyshomeostasis, mitochondrial dysfunction, exhaustion of redox defence systems, ultimately signalling to initiate programmed cell death cascades.



Scheme 1. Neurodegenerative disorders are multi-factorial disorders. oxidation involved

2.Sources of oxidative stress in neurodegeneration

2.1 Mitochondria

Deficits in cell bioenergetics are a common in most neurodegenerative diseases as well as in aging. Alzheimer's disease, Parkinson's disease, Friedrich ataxia, among others, also share some aspects of impairment of glucose homeostasis and insulin

resistance [2]. Mitochondria are well-known to be affected in ND, and mitochondrial dysfunction has been long ago accepted as a potential generic deleterious mechanism in neurodegeneration; this is not surprising as mitochondria perform central functions in cell life. Mitochondria are both producers and highly vulnerable targets for the various types of ROS. This is especially true for the brain-an organ with very high turnover, oxygen consumption, end point differentiation. Therefore, cell death, although adult neurogenesis has been confirmed, is terminal.

2.1.1 ETC and matrix ROS production

The value of the mitochondrial membrane potential is controlled by the rate of the electron flux along the electron transport chain. Interestingly, ΔΨm does not necessarily directly correlate with the ATP and ROS production levels. Commonly observed in ND is the reduction in ΔΨm, but also is the hyperpolarisation of mitochondria[3], the latter being a compensatory mechanism, aiming at stabilisation of the mitochondrial membrane potential, as its drop signals apoptotic signalling cascade initiation, ultimately leading to neuronal loss. In this case ΔΨm depends on the reversal of the function of the ATP synthase which, back-flushes protons while consuming ATP. Although reduction of Complex I activity has been reported for most of the genetic models of PD, it is now accepted that ATP levels reduction is not the main reason for development of pathology, but rather it is the increased electron leak and consequent increase in superoxide production and oxidative stress. Indeed, higher ROS production, originating as a dysfunction of the electron transport chain has been reported for PD, AD, ALS, PSP.

Reduction of the activity of complex I maybe a result of substrate availability shortage, especially for complex I (NADH), where NADH might be dragged away to the pentose phosphate pathway, as a reducing equivalent, replenishing the GSH pool.

Another possibility might be that the structural and assembly defects of the enzymatic complex underlie the reduced activity of complex I. In agreement with the latter, complex I of the electron transport chain (ETC) has been reported to be one of the most often affected mitochondrial enzymatic complexes in ND, both in the genetic as well as in the sporadic forms of the disease in PD [4], [5], [6], [7], [8], AD [9], as well as Leigh syndrome [10], [11], [12], MELAS syndrome [13], [14], MERRF syndrome [15], [16], Leber hereditary optic neuropathy [17], [6]. In support of this fact, inhibitors of ETC complexes I and III have been used earlier to develop chemical models of ND, e.g. rotenone and MPTP for PD [18], [19], [5].

To assist with oxygen and metabolic conversion and signalling many ROS-producing and converting enzymes exist in the matrix of mitochondria: α-ketoglutarate dehydrogenase (KGDHC), pyruvate dehydrogenase complexes (PDHC), aconitase, to name a few, and mutations and reduced activity of these enzymes have been reported for many types of neurodegenerative diseases [20], [21], [22].

Beta-oxidation is the intermediate step of the catabolic pathway for lipid degradation and utilisation. Through beta-oxidation turnover the free fatty acids (FFA) become suitable for utilisation in the TCA in the form of Acetyl-CoA. Indeed, higher FFA levels critically increase the probability of ROS production and lipid peroxidation, that may lead to lipotoxicity through increased levels of calcium deregulation, mitochondrial dysfunction and cell death-features that are very similar in, and possibly linking ND and diabetes type 2 [23], [24].

Indeed, severe defects in beta-oxidation have been associated with ROS generation and the subsequent development of neurodegenerative diseases [25], [26]. On the other hand, defects in mitochondrial fatty acid synthesis and lipoic acid in particular, lead to deficiency in functional iron-sulphur clusters in the mitochondria and to the

development of CoPAN, PKAN, MEPAN syndromes (types of **N**eurodegeneration with **B**rain **I**ron **A**ccumulation; NBIA) [27], [26].

2.1.2 Mitochondrial ROS-producing enzymes

Monoamine oxidases types A and B (MAO A/MAO B) and (COMT) are key enzymes in the catabolism of biogenic monoamine neurotransmitters (dopamine, serotonin, norepinephrine, epinephrine, etc.) and xenobiotic amines, which produce hydrogen peroxide (H_2O_2) as a by-product. They play an important role in physiological signalling cascades, e.g. epinephrine (adrenaline) and dopamine, both activate directly MAO B to induce calcium signal through the production of H_2O_2, lipid peroxidation and consequent phospholipases activation in astrocytes [28], which in the case of adrenaline further leads to vasoconstriction of the nearby situated blood vessels[29],. Both overproduction and reduced production of dopamine and higher generation rates of H_2O_2 would have essential part in the development of neurodegenerative diseases. In agreement with this, it has been reported that increase in dopamine turnover inhibits the electron flow via the ETC (mitochondrial respiration) possibly through the generation of H_2O_2 and hydroxyl radical ($HO^{\cdot -}$) [30], by the activation of MAO [28] and/or by the thiol redox state of plethora of mitochondrial enzymes (e.g. complexes I, II, III, V, isocitrate dehydrogenase, alpha-KG, aconitase, glycerol-3-phosphate dehydrogenase (GPDH); dihydroorotate dehydrogenase (DHOH) and cytochrome b5 reductase (B5R) or mARC [31], [32], [33]. Given the fact that the tricarboxylic acid cycle (TCA)/PPP and the ETC/OxPHOS are tightly coordinated directly through the succinate dehydrogenase (complex II) and through enzymatic substrates that are at the same time reducing equivalents in many redox reactions (NADH, $FADH_2$, NADPH), it is not surprising that TCA/ETC are also tightly redox coupled and vulnerable to transposing oxidative damage to each

other. While it is known that MAO-B levels increase with ageing [34], and in the cases with AD while MAO-A decreases [35], the situation in PD is still controversial. In PD the most susceptible to cell loss are the striatal dopaminergic neurons, where the burden of oxidation is very high: on one side constant exposure to exogenous dopamine, which could also autooxidise to produce superoxide; and on the other dopaminergic neurons are exposed to H_2O_2 produced by MAO while metabolising dopamine.

Interestingly MAO-A inhibitors (selegiline, rasagiline) not only inhibit degradation of dopamine and H_2O_2 formation , but also stimulate the expression of neurotrophic factors-NTFs (BDNF, GDNF, MANF, CDNF) *in vivo* and *in vitro* which in long term account for the recovery of nerve tissue [36], [37].

Gene polymorphism has been reported for MAO A/MAO B and COMT in PD and AD patients, and whether genetic or stress-induced, there is a great potential for this variation to alter gene regulation and consequently to impact function [38]. Catechol-O-Methyltransferase (COMT) is another enzyme that catalyses the conversion of active catecholamines (dopamine, epinephrine, norepinephrine, estrogens) into inactive metabolites and thus facilitates their excretion, while mitochondrial aldehyde dehydrogenase (ALDH2) catalyses the metabolism of catecholaminergic metabolites (DOPAL and DOPEGAL) and the major products of lipid peroxidation – 4-hydroxynonenal (4-HNE), malondialdehyde, acrolein and acetaldehyde [39]. Reduced activity of both COMT and aldehyde dehydrogenase 2 (ALDH2), conferred by genetic polymorphism provide an insight into the interactions between enzymes metabolizing biogenic monoamines in the pathogenesis of PD and AD [40], [41], [42], [43], [44]. In addition, catecholestrogens could undergo redox cycling to further produce ROS, generate electrophilic ortho-quinone intermediates, and to damage surrounding

biomolecules and to further reduce thiols. There is an emerging body of evidence that incomplete metabolism and consequent detoxification of the products of catabolism of monoamine neurotransmitters might contribute to the mechanism of neurodegeneration. Interestingly, selegeline (Deprenyl), a selective MAO-B inhibitor that is widely prescribed to PD patients, has been shown to directly and very potently attenuates oxidative stress in cellular models of PD [45].

Superoxide dismutases, in particular the Mn-SOD (SOD2) and to a lesser extent the Cu-Zn SOD (SOD1) are essential transition metal-containing superoxide-detoxifying mechanisms with mitochondrial localisation [46]. Mutation of SOD1 has been found to have a direct link to amyotrophic lateral sclerosis (ALS) pathology [47]; [48]; [49], and low expression levels and activity in AD [50].

Mitochondrial amidoxime-reducing component (mARC1/2) are a molybdenum-containing enzymes involved in the regulation of nitric oxide synthesis [51], where electrons are transferred from NADH to cytochrome b5 reductase and via cytochrome b5 to mARC. ROS production of mitochondria can also be modulated by NO by signalling through reversible binding to Cytochrome C oxidase (complex IV), and subsequent inhibition of the electron transfer and generation of superoxide. NO might be either diffusing to mitochondria from eNOS (endothelial nitric oxide synthase), produced by direct nitrate reduction or generated on cite by mitochondrial isozyme [52],[53] . Nitric oxide may then interact with iron-sulphur clusters of the electron transport chain. Further, nitric oxide could react with superoxide to form peroxynitrite ONOO-, which is a potent oxidant and a major endogenous neurotoxin.

2.1.3 Calcium buffering capacity of mitochondria as regulator of ROS production

Mitochondria are also important calcium buffering organelles, that modulate the cytosolic calcium concentration, together with other mechanisms, to avoid cytotoxic long-term elevated levels. Mitochondrial calcium buffering capacity is controlled by the mitochondrial membrane potential, on one side, and by the proper functionality of mitochondrial calcium uniporter (MCU) and the mitochondrial sodium calcium exchanger (NCLX), that control calcium uptake and release, on the other [54, 55]. Defects in calcium homeostasis and subsequent ability of mitochondria to buffer increased cytosolic calcium have been described in the literature for many types of ND [56, 57, 58].

2.1.4. Mitophagy/autophagy

Mitophagy is a mechanism for organelle quality control responsible for the degradation of damaged/depolarised mitochondria. It is known to be triggered by mild oxidative stress and as this process becomes defective with advancement of age it is thought to be one of the causal mechanisms for ageing and the development of age-related neurodegenerative diseases. Mitophagy plays an essential role in reducing the mitochondrial ROS production by maintaining mitochondrial quantity and quality [59]. Moreover, mitophagy is the mitochondrial population correcting process that removes the excessive-ROS-producing mitochondria [60]. Mutations of PINK1, PARK2 (which encodes parkin) or PARL genes, tightly involved in mitophagy are connected to the development of early onset PD or Leigh-like syndrome [61]. Defective mitophagy/autophagy have been shown also for AD, HD, and ALS [62-64].

2.1.5 PTP opening and cell death

Mitochondria appear to be directly or indirectly linked to all postulated mechanisms of toxicity associated with ND. When the mitochondria membrane potential, as a

direct sensor for the integrity and functionality of the coupling of ETC with OXPHOS, had no chances to be stabilised within a very narrow range, together with accumulation of mitochondrial calcium and higher rates of lipid peroxidation, it triggers the opening of the mitochondrial permeability transition pore (mPTP). Although the exact molecular constituents of this high conductance "mega-channel" are still highly disputable, it is well accepted that the mPTP opening is the point-of-no-return, beyond which the cell undergoes programmed cell death. As almost all ND diseases have in common mitochondrial dysfunction, calcium dyshomeostasis and higher rates of ROS production it is also accepted as a rule of a thumb that mPTP opening is part of the mechanism of ND. Indeed, mPTP opening has been reported for many models of ND [65], [66]. Earlier studies by Lemaster et al. have proposed the opening of the mPTP to be also a trigger for the initiation of mitophagy/autophagy [67], [68], but this subject remains still highly debatable.

2.2 Cytosolic ROS producing/converting enzymatic and non-enzymatic systems

2.2.1 NADPH Oxidase

NOXs/DUOXs (NADPH oxidases) are enzymatic super complexes, situated on the plasma membrane that serve as a local source of superoxide [69]. They transfer electrons across the plasma membrane and are coupling these to molecular oxygen. Thus, they may serve as an oxygen sensor [70], and play various signalling roles in the regulation of the innate immunity, gene expression [71], [72], signal transduction [73], cellular proliferation, differentiation and growth [74], [75], and further to the initiation of cell death [76], [77], [78]. ROS can regulate ion channels of the plasma and organelle

membranes [79], [80], [81], [82]. NOXs/DUOXs can be activated through a calcium signal. However, the opposite is also true and the superoxide, released by NOX could release calcium from internal stores [83], [84]. Inhibition of NOX have been reported to be useful for reducing oxidative stress and improving cognitive function in ND [85], [86],[87], [88], [89], [90], [91].

2.2.2 Xanthine Oxidases

Xanthine Oxidase/Xanthine dehydrogenase (XDH) are isozymes of xanthine oxidoreductase that are involved in the reactions of purine catabolism, converting hypoxanthine to uric acid through xanthine [92]. Although XO is a serious producer of superoxide, especially in the time of mild hypoxia [92], not much information is available for its role in ND. Most information about XO involvement in the neurodegenerative cascades were derived from inhibitor analysis where XO inhibitors, allopurinol and oxypurinol, have been able to attenuate the ROS generation in HD, and furthermore protect from neuronal cell death in cellular models of PD and AD [93], [94]. Further to that, overexpression of XO has been reported for various ND, including AD [93].

2.2.3 Nitric oxide synthase

Nitric oxide is a key signalling molecule in the brain; it works both intra- and extracellularly to regulate the vascular tone, neuronal signalling, and response to infection. Inducible NOS plays a well-described role in neurotoxicity in ND [95], [96], [97], [98]. Disease-involved proteins can also stimulate the release of NO [99]. Further, excess NO can S-nitrosylate various proteins that play key role in ND, namely parkin, complex I from the ETC, drp-1, protein disulphide isomerase, etc. [100].

2.3 Cytosolic calcium as a trigger of oxidative stress

Intracellular calcium concentration has to be kept low in order to enable cell calcium signalling. Several calcium transport mechanisms are involved in the compartmentalisation of intracellular calcium and maintenance of calcium gradients: Na^+/Ca^{2+} exchanger (NCX) and Ca^{2+}-ATPase (PMCA) situated on the plasma membrane and the Sarcoendoplasmic Reticulum Ca^{2+}-ATPase (SERCA) from the ER work together with the mitochondrial calcium transport mechanisms described earlier and with the calcium-binding protein family (parvalbumin, calbindin, calretinin, calmodulin), which all work together to keep intracellular calcium levels low.

Defects in all mechanisms, controlling for adequate calcium concentrations in the neurons have been reported for many ND [101], [102], [103], but especially is this true for oxidative damage of this proteins [104], [105], [106].

Higher cytosolic calcium activates the NADPH Oxidase, a massive production of superoxide, that is rapidly turned into H2O2 or molecular oxygen by the superoxide dismutase (SOD). In ND it is often reported dysfunction in the described transport mechanisms or pore-forming properties of misfolded proteins that lead to increased cytosolic calcium levels and ROS production rates and subsequent activation of mPTP opening, ultimately resulting in neuronal cell death [1], [107], [108].

2.4 Lipid peroxidation

Superoxide produced in NOX is a very short-lived type of ROS (10^{-9} s), and because of its high reactivity, it is either converted enzymatically to H2O2 or by interacting with nearby situated molecules it forms large variety of toxic moieties including peroxides and carbonyls to damage protein or nucleic acids.

The brain is an organ enriched in polyunsaturated fatty acids (PUFA). The PUFA content enables the fluidity of brain cell membranes and allows for exertion of various signalling processes. PUFA are especially prone to oxidation due to the presence of bis-allylic hydrogen atoms, that are easily abstracted, both enzymatically and through auto-oxidation, converted to lipid radicals with signalling function through dramatic activation of phospholipases PLA2, PLC, PLD [109,110]. Lipid peroxidation is a physiological process that enables signalling functions of the cell. For example, breathing frequency is regulated through lipid peroxidation while mitochondria serve as an oxygen partial pressure sensor [111]. However, excessive rates of lipid peroxidation are sign of oxidative stress and are seen in all types of neurodegenerative disorders, e.g. PD, AD, NBIAs -PANK2 and PLA2G6-associated, FTDP-17 or ALS [3, 112, 113 114].

Major products of enzymatically-mediated lipid peroxidation are the lipid hydroperoxides of arachidonic acid- 15-hydroperoxy-AA-PE (HOO-AA-PE) that have recently been found to be the signalling trigger for initiation of ferroptosis -specific type of iron and lipid peroxidation-dependent programmed cell death [115, 116]. Indeed, 15-hydroperoxy (Hp)-arachidonoyl-phosphatidylethanolamine (15-HpETE-PE) have been found in PLA2G6-associated neurodegeneration [117].

Elevated levels of malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), acrolein and increased rates of lipid peroxidation (LPO), as well as reduced glutathione content, all can serve as sensitive markers for oxidative stress and have been largely reported for brain tissues of ND patients [118, 119]. Increased rates of lipid peroxidation have been involved in almost every cell model of ND, for example PD, Friedrich's ataxia, FTD, ALS, PSP [120 121 122]. Moreover, it is known that misfolded and aggregated

alpha-synuclein leads to ferroptosis via activation in lipid peroxidation in the presence of transition metal ions, including iron [123].

2.5 Arachidonic acid second messenger system

Another potential source of ROS is the arachidonic acid second messenger system that converts the calcium-dependent signal with the help of PLA2, 5-lipoxygenase (5-LOX), cyclooxygenase COX and cytochrome P450 (CytP450) into neuroinflammatory signal in the form of leukotrienes, hydroxyeicosatetraenoic acids, epoxyeicosatrienoic acids, hydroperoxyeicosatetraenoic acids, prostaglandins, thromboxanes and lipoxins [124], [125], [126]. In this type of signalling reactions phospholipases trigger phospholipid signalling cascade that regulate inflammatory response with final reduction of these radical signalling intermediates by GSH or GSH-S-transferase [127], that could lead to reducing equivalent pool depletion in ND. Indeed, in ND, lipid peroxidation, depletion of endogenous thiols and neuroinflammation are part of the greater picture. AA also directly activates NADPH oxidase to produce superoxide, independent of eicosanoid biosynthesis [128]. Arachidonic acid can also regulate the activity of ion channels through oxidation of the protein thiol switches [129]. On the other hand, phospholipases are membrane lipid turnover regulating enzymes that use only oxidised lipids as substrates [110]. And least, but not last, NOX plays an instrumental role in the erastin -induced neuronal death, which has been termed ferroptosis [130]. Erastin is an inhibitor of cystine/glutamate antiporter (xCT) and thus glutathione synthesis, and an activator of VDAC (voltage-dependent anion channels in mitochondria). Ferroptosis is a unique type of non-apoptotic programmed cell death, that is dependent on the presence of three factors: lipid peroxidation, iron involvement and defect in the redox status.

2.6 Transition metals dyshomeostasis

Transition metal homeostasis is severely perturbed in neurodegeneration. Metal trafficking defects, resulting in inappropriate distribution underlies the metal hypothesis of ND. Metal ion depositions could be one of the diagnostic criteria for brain tissue from ND patients, while widely variable, there are some, i.e. iron depositions in substantia nigra PD, PSP, MSA [131] or in the globus pallidus for NBIA and neuroferritinopathy [132]. Copper levels have been reported to be reduced in PD and PSP, but elevated in HD and AD, and zinc ions increased in PD [131].

The implication of defect metallostasis in ND has been reported widely. Additionally, transition metal chelators have been shown extensively to reverse pathology in ND animal models [133], [134], [135] and in cellular models of ND [136]. Further, targeting transition metal interactions with misfolded proteins by metal chelators have also been shown to reverse aggregation in tissue from ND patients [137], [138].

Metal-induced aggregation of critical proteins has been well documented. For example Cu and Zn induce aggregation of β-amyloid [139], [140], while iron is instrumental in the aggregation of alpha-synuclein [141] , β-amyloid [142] and tau [143]. Further to that, it has been shown that misfolded alpha-synuclein forms soluble aggregates by adopting a beta-sheet conformation to facilitate ROS production in a cell-free environment [65], [144]. One of the possible explanations to this phenomenon is the presence of trace transition metal ions in the buffer.

There is a separate classification of neurological diseases where iron accumulation in the basal ganglia and extrapyramidal symptoms are the main classification criteria – this group of diseases is termed **N**eurodegeneration with **B**rain **I**ron **A**ccumulation (NBIA) [145]. Ten NBIA forms are widely accepted to be caused by mutations in the following genes: (PANK2), (PLA2G6), (WDR45),(C19ORF12), (FA2H), (ATP13A2), COASY, FTL1, CP, and DCAF17 [146]. However, NBIA share common features with the

rest of the neurodegenerative disorders, either genetically predisposed or sporadic: defect iron transport and redistribution mechanisms, protein aggregates, lipid peroxidation, mitochondrial dysfunction and disturbed dynamics, and defect mitophagy/autophagy [146], [112], [147], [145].

Iron, copper, zinc, and manganese ions are cofactors of metalloenzymes and metalloproteins from the mitochondria. These include the mitochondrial enzymes and Fe/S clusters of the ETC, mitoferrin 1/2, voltage-dependent anion channel (VDAC1), aconitase, sterol carrier protein 2, mitochondrial NAD-dependent deacetylase sirtuin-3 (SIRT3), FXN, cysteine desulfurase (NFS1), mitochondrial ferritin (FtMt) [148].

Thus, when metal co-factors are misplaced or metal ion transport hindered, transition metal ion–catalysed reactions involving iron, copper, etc. (i.e. Fenton or Haber-Weiss reactions) become major producers of ROS/RNS in ND. Fenton reaction is a type of iron-catalysed chemical conversion of H_2O_2 into highly reactive free radicals that further attack lipids, proteins and DNA. In the “conventional” Fenton reaction the most “toxic” and highly-reactive radical, the hydroxyl radical, and a hydroxide ion are produced from hydrogen peroxide in the presence of catalytic divalent transition metal ions (iron or copper). In the Haber-Weiss reaction, also called superoxide-driven Fenton reaction, the conversion of hydrogen peroxide is being coupled to a reduction of superoxide radical to molecular oxygen.

Defect metallostasis has been described to have direct amyloidogenic consequences on disease-related proteins like alpha-syn, beta-amyloid, tau, presenilin, and oxidative stress have been shown to have a pivotal role in development of ND [118]. Finally, iron is a key factor in a recently described form of neuronal cell death, causal for neurodegeneration- ferroptosis [123].

2.7 Misfolded proteins as a source of ROS

The major histopathological hallmark of neurodegenerative disorders is the presence of misfolded and aggregated amyloidogenic protein deposits. However, the type of protein, as well as clinic and histology often overlap. Thus, dysfunctional alpha-synuclein causes not only Parkinson's Disease, but also Lewi Body Dementia and Multiple Systems Atrophy, that are termed synucleinopathies. β-amyloid could be observed histochemically not only in Alzheimer's Disease, but also in Lewi Body Dementia, Primary Progressive Aphasia, Frontotemporal Dementia. Neurofibrillary tangles of hyperphosphorilated tau are evident in AD, Progressive Supranuclear Palsy, Primary Progressive Aphasia, Frontotemporal Dementia, commonly termed tauopathies. Amyotrophic Lateral Sclerosis, Frontotemporal Dementia or the combined form ALS/FTD is characterised by cellular redistribution and therefore dysfunction of the FUS or the TDP-43 proteins. However, the TDP-43 could be also detected in brains not only of ALS and FTD patients, but also in AD and PPA.

The mutated protein huntingtin is linked to the development of Huntington's disease (HD) that features polyQ (poly glutamine) repeat expansion of the Htt gene, and characterised by the massive striatal neuronal loss and Htt aggregate formation [149, 150,151]. However, PolyQ expansion is associated also with other neuromuscular degenerative diseases, such X-linked spinobulbar muscular atrophy (SBMA) and various spinocerebellar ataxias (SCA1, 2, 3, 6, 7 and 17) [152, 153]. Thus, the majority of neurological and neurodegenerative diseases are also classified as proteinopathies [154]. The primary amyloid-forming proteins are in general proteins with amorphous structure that adopt an atypical highly ordered, insoluble, beta-sheet-rich structure,

which later in time forms fibrils and intractable amyloid depositions, associated with ND (amyloid plaques, Lewi bodies, NFT) [154].

Indeed, the intermediate (soluble) aggregates of abnormal alpha-synuclein, tau, beta-amyloid, etc are highly neurotoxic [155], [156], [120], [157] through initiation of oxidative stress, mostly through activation of NOX and activation of cell death cascades [158], [108], [159].

Thus, protein misfolding and aggregation of proteins of otherwise physiological function [160] are more likely to lead not only to loss of physiological protein function, but additionally to a toxic gain-of-function: for example – alpha-syn, membrane channel-like activities that compromise plasma and organelle membrane integrity and lead to mitochondrial PTP opening [65].

It has been known for a long time that overexpression of alpha-synuclein gene leads to overproduction of ROS in genetic models of ND [136]. Recently we have found a physiological role for alpha-synuclein in the mitochondria [161], besides the proposed functions in the synapse. Thus, overexpression of the SNCA gene leads to a misfolding and aggregation of alpha-synuclein-which leads to mitochondrial dysfunction, ROS generation at the site of execution of physiological function [65].

Similarly, mutant superoxide dismutase 1 forms aggregates in the brain mitochondrial matrix of amyotrophic lateral sclerosis mice [162], where it further causes mitochondrial abnormalities and neurotoxicity [163]. It has been reported that in SOD1 mutant aggregation leads to higher rates of superoxide production in a VCP-related human model of ALS [164], probably because of SOD 1 “loss-of-function”.

2.8 Reduced cellular redox defence systems activity in ND

Importantly, many of these redox defence enzymes (e.g., catalase, GPX1, GPX4, PRX3, and PRX4) are physically localized to the place of higher oxygen turnover-mitochondrial matrix, where they oppose the constant production of ROS [165], [166], [167], [168]. However, every exhaustion of those antioxidant defence mechanisms renders mitochondria, and all aspects of their essential functions, extremely vulnerable to the action of ROS and leads to mitochondrial dysfunction.

2.8.1 Endogenous antioxidant molecules

The non-enzymatic antioxidant defence system includes various small molecules like GSH, urea, tocopherols, retinols, bilirubin and lipoic acid, capable of direct scavenging of free radicals or acting as co-factors on antioxidant or detoxifying enzymes. Low levels of endogenous antioxidant molecules were reported for many types of neurodegeneration.

Glutathione (GSH) is the major thiol-containing small molecule with the essential role to scavenge any water-soluble ROS, both enzymatically and non-enzymatically, thus mediating the redox signalling between various cellular compartments [169], [170], [171]. GSH depletion therefore, results in a variety of pathological conditions and leads to degeneration [171], [172], [173], [174], [172]. Most neurodegenerative diseases are accompanied by severely decreased GSH levels in both neurons and astrocytes, [175], [176], [177].

2.8.2 Enzymatic redox defence systems

Brain cells are equipped with various thiol-dependent redox systems, including the GSH-glutaredoxin (Grx) system, consisting of NADPH, glutathione reductase (GR), and glutathione (GSH) and the thioredoxin system which comprises of thioredoxin (Trx), thioredoxin reductase (TrxR), and NADPH [178]. Because bioenergetics is tightly

coupled to ROS production, in neurodegeneration, due to a failure of energy supply to the highly energy-demanding brain tissues, the redox balance is shifted to oxidation, since reducing equivalents are dragged over to fill energy gaps.

Further redox defence enzymes include superoxide dismutase (SOD), catalase (CAT), GPx, and peroxiredoxin (Prx). Soluble superoxide dismutase (SOD)- Cu/Zn-SOD-SOD1 and SOD3- can catalyse the conversion of superoxide to H2O2, a well-known signaling messenger. Several mutations of Cu, Zn-SOD gene have been reported to be associated with ALS [179]. Additionally, oxidative modification and aggregation of the enzyme have been observed in PD and AD [180].

Peroxisomes are small cellular organelles that play important role in cellular lipid metabolism and are redox and metabolic signalling hub between ER and Mitochondria [181]. They contain several essential antioxidant enzymes, e.g. catalase, super oxide dismutase 1 (SOD1), peroxiredoxin 5 (Prx5), and glutathione peroxidase (GPx), glutathione S-transferase kappa, 'microsomal' glutathione S-transferase, and epoxide hydrolase 2, Lon protease 2 (LonP2), which all balance out the excessive peroxisomal oxidase-generated ROS [182]; [181], [183], [184]. While congenital paroxysmal defects are molecular determinants of neurodegeneration-like phenotype development, e.g. X-linked adrenoleukodystrophy (X-ALD), declining function of the ageing peroxisomes could be one of the triggers of sporadic forms of neurodegenerative diseases. Thus, defect peroxisomal functions have been associated with ALS [185], AD [186], PD [187], Zellweger syndrome [188].

2.8.3 Nrf-2

An intrinsic master regulator of the constitutive antioxidant defence of the cell is Nrf-2 (Nuclear factor erythroid 2-related factor 2), which further regulates mitochondrial

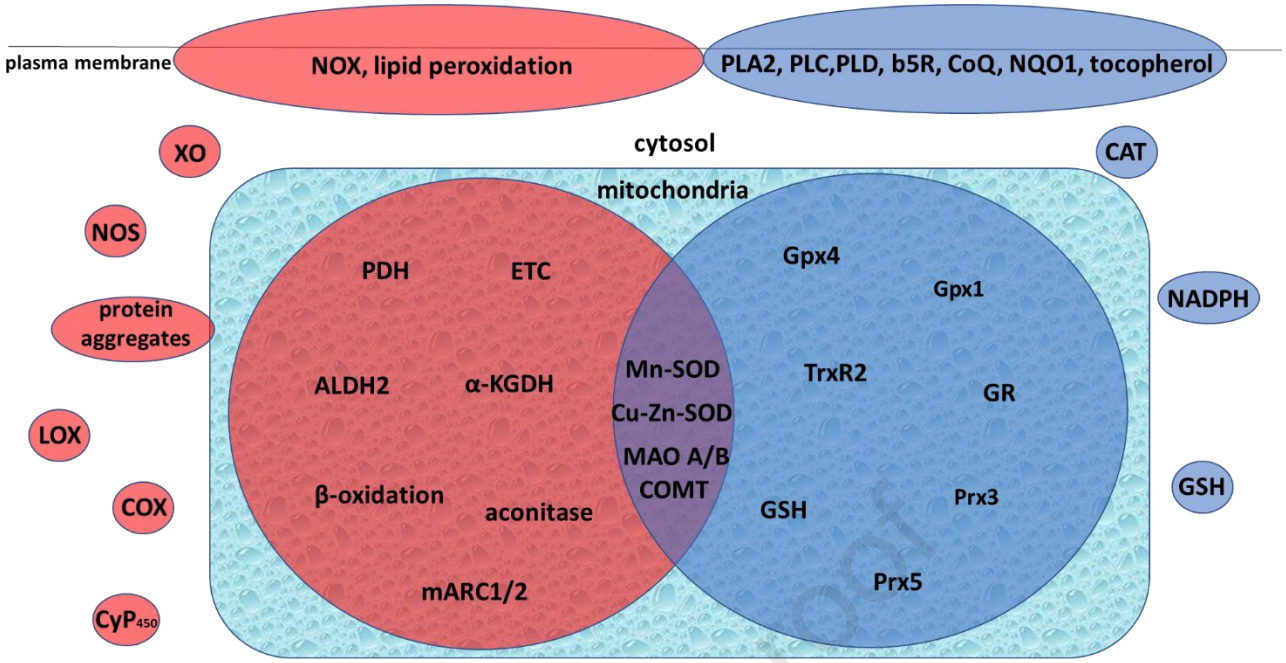
bioenergetics (OxPhos and β-oxidation), superoxide production through NADPH Oxidase, glutathione-synthesizing or -regenerating enzymes and NADPH producing enzymes from the pentose phosphate pathway to stabilise GSH levels. As both mitochondrial defects and oxidative stress are characteristic of all neurodegenerative disorders, activation of Nrf-2 is a very promising mechanism for opposing the higher ROS production rate if ROS in ND and maintaining adequate redox status, in the neurons, which enables survival. Indeed, there have been shown various positive effects of Nrf-2 activators in animal models and cellular models of neurodegenerative diseases such as ALS/FTD, PD, AD, HD or FRDA [189], [190], [191], [192], [193]. Nrf-2 activators are currently tested and show very promising results in clinical trials for FRDA, AD and HD [194], [195]. Nrf-2 activation has been shown to restore redox homeostasis, mitochondrial bioenergetics and biogenesis, to enhance rates of autophagy and proteasomal degradation of misfolded proteins, while opposing neuroinflammation and oxidative damage [196], [197].

2.8.4 ***PRDX***

PRDX is a protein superfamily of thiol-specific peroxidases, enzymes with antioxidant function that catalyse the reduction of hydrogen peroxide and organic hydroperoxides to water and alcohols. PRDX3, specifically localized to the mitochondria, is essential for maintaining the mitochondrial mass and mitochondrial membrane potential. Thus, Ebselen, a PRDX mimetic has been shown to improve in models of ND [198]

2.9 Plasma membrane redox system (PMRS)

PMRS is a system of enzymes and metabolites, featuring ubiquinone (CoQ) and alpha-tocopherol, that utilise the electrons pumped by the NAD(P)H and recover previously oxidized antioxidants back to their reduced states and thus protects against lipid peroxidation and apoptosis induced by oxidative injury. PMRS accomplishes it protective role by delivering more NAD+ for ATP production (through glycolysis) via the transfer of electrons from intracellular reducing equivalents to extracellular acceptors. The enzymes' of the PMRS (cytochrome b5 reductase (b5R), reduced form of coenzyme Q (CoQH2), NADH-quinone oxidoreductase (NQO1) proper functioning is affected by ageing and may well play role in the development or further progression of neurodegenerative diseases [199, 200]. Indeed, PMRS components have been reported to be down-regulated in different models of ND. Lower NQO1 expression has been shown for 3 × transgenic mice harbouring presenilin 1 (M146V), a precursor of amyloid protein (Swe), and tau (P301L) mutations [201, 202]. Also, long ago it has been known that CoQ and tocopherol are decreased in mitochondria from different tissues by up to 50% in aged patients and people with AD [203].



Scheme 2. Oxidising and reducing mechanisms in the mitochondria and in the cytosol

2.10 Activated microglia as a source of ROS

Microglia are the major resident type of macrophage-like cells in the CNS and as such they account for the first line of active immune defence. Microglia are also playing essential role in synaptic organization, neuronal excitability, neuronal support, myelin turnover, debris removal as well as brain protection and repair [204]. Indeed, neuronal debris can activate microglia, leading to the release of different inflammatory factors, such as, pro-inflammatory cytokines, chemokines, etc., along with ROS and reactive nitrogen species (RNS). Thus, neuroinflammatory response is considered a crucial factor in the progression of ND. Early evidence from *post mortem* analysis of patient' tissues showed that activated microglia localise in the vicinity of neuritic plaques in AD [205] or in substantia nigra in PD [206] tissue. Several studies have shown that early alterations in protein aggregation and neuroinflammation are fact in FTLD, AD and ALS [207], [208], [209], [210]. In chemical PD animal models, the toxins used (6-OHDA, MPTP, LPS), all evoke both microglial activation and neuronal death [211], [212], [213] In a vicious cycle, the overactivated

microglia release pro-inflammatory cytokines through activation of JAK/STATs and NFkB pathways, yielding TNF-α, IL-1β and iNOS, which in turn triggers further uncontrolled inflammatory response and neuronal cell death, and accelerate neurodegeneration.

2.11 Excitotoxicity

Excitotoxicity [214] is the overactivation of ionotropic glutamate receptors, i.e. NMDA, AMPA and kainate receptors, followed by further activation of metabotropic glutamate receptors, activating VGCC and IP3 and DAG pathways, resulting in calcium overload, impairment of metabolism, and disrupted ionic gradients [215]. High cytosolic calcium activates arachidonic acid second messenger system and NOX which leads to massive production of ROS. Calcium further stimulates enzymatic degradation of DNA and proteins. In FTD for example, overproduction of mitochondrial ROS in neurons alters the trafficking of specific glutamate receptor subunits via redox regulation. Increased surface expression of AMPA and NMDA receptors leads to impaired glutamatergic signaling, calcium overload, and excitotoxicity[216]. Importantly, extracellularly applied 4R tau similar picture in healthy neurons [216]. It has been long known in the case of ALS that SOD1 mutant motoneurons are more susceptible to excitotoxicity [217]. In ALS, for example, among the multiple proposed mechanisms for motoneuron degeneration in the spinal cord, brain stem and cerebral cortex, the AMPA and NMDA receptor-mediated cell death and impairment of the glutamate-transport system have been suggested to play a central role [218]. NMDA receptor-mediated mitochondrial Ca (2+) overload in acute excitotoxic motor neuron death is a mechanism distinct from chronic neurotoxicity after Ca^{2+} influx.

There are several possibilities for originating of excitotoxicity: 1) A damaged neuron, observed in the course of the development of ND, could well be *per se* the physical source of excitotoxicity. 2) High levels of glutamate meanwhile are well accepted to be a direct trigger of excitotoxicity. 3) Hypoxic-ischaemic conditions in the brain that result from inadequate or impaired blood flow, e.g. vascular dementia or stroke, inevitably lead as well to excitotoxicity [219], [220]. 4) Mitochondrial toxins block ETC and seize the ATP production necessary for the reuptake of glutamate and restoring of plasma membrane ionic gradients.

2.12 Synaptic disruption as a source of ROS

Ageing is accepted to be the largest risk factor for developing ND [221]: genomic instability, telomere shortening, epigenetic modifications, proteostasis deprivation, mitochondrial dysfunction, cellular senescence, defect nutrient sensing, stem cell depletion, all could lead to age-dependent synaptic modifications, such as reduced intensity and timing of transmitter release, and ultimately to altered intercellular communication. ROS, and mitochondrial ROS in particular, are redox regulators of physiological functions [109]. Mitochondrial ROS regulate glutamatergic signaling in the brain and thus, whenever the neuron is brought out of redox balance in the course of ND, this will result in altered neuronal excitability, synaptic morphological changes, and neurotransmission deficiencies. ND could therefore also be considered synaptopathies. Synaptic dysfunction and altered excitability have been well documented for ALS, PD, AD [222],[223],[224]and pre- and postsynaptic proteins being recognized to have a potential to serve as early biomarkers of ND [225],[226].

H2O2 is the ROS with the longest lifespan and because of that and despite its limited membrane diffusion it can act as a signaling molecule. It has been found that H2O2 at low micromolar concentrations is able to inhibit both, spontaneous and evoked

transmitter release and this effect was not associated with lipid peroxidation, suggesting a pure signaling role of H2O2 [227]. Further, age-dependent effects on the protective capacity of several antioxidant enzymes: reduced activity of catalase and glutathione peroxidase, and increased activity of glutathione transferase have been documented [228]. Age-dependent brain tissue susceptibility to ROS insult could be explained by the altered neuronal signalling processes and by the availability of antioxidant enzyme defence.

3.0 Conclusions and perspectives

Oxidative stress has been shown to be involved in all neurodegenerative disorders, therefore, despite previous negative outcomes of clinical trials with antioxidants, probably because of lack of specificity or low bioavailability of synthetic modifications, this is still one of the most promising therapeutic targets for ND. Potential therapeutic approaches, targeting oxidative stress, should include more modern strategies to target mitochondria, protein aggregation, lipid peroxidation, e.g., mitochondrially -targeted antioxidants, mitochondrial-membrane-release scavengers, mitochondrial substrates, targeted enzyme mimetics, lipid radical traps, latest-generation targeted metal chelators, gene therapy, etc.

Besides that, stimulation of clearance mechanisms, i.e. autophagy/mitophagy induction, that in humans could be achieved through more natural processes like fasting or calorie restriction, exercise, and mild hypoxia (high altitude elevations) should occur in parallel. However, in the future, all multifactorial diseases and especially neurodegeneration, might need a more bespoke therapy approach, combining the personalised medicine with multitarget neuroprotective compounds,

aiming at scavenging free radicals, taming ROS-producing enzymes, activating the intrinsic redox defence forces, while chelating loose transition metals, all at once [229].

Hence, one of the biggest challenges for the future therapeutic agents is to be able to distinguish between physiological and pathological levels of ROS; and target the excess ROS without interfering with cellular signalling.

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