The contribution of an imbalanced redox signalling to neurological and neurodegenerative conditions

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Abstract

Nitric oxide and other redox active molecules such as oxygen free radicals provide essential signalling in diverse neuronal functions, but their excess production and insufficient scavenging induces cytotoxic redox stress which is associated with numerous neurodegenerative and neurological conditions. A further component of redox signalling is mediated by a homeostatic regulation of divalent metal ions, the imbalance of which contributes to neuronal dysfunction. Additional antioxidant molecules such as glutathione and enzymes such as super oxide dismutase are involved in maintaining a physiological redox status within neurons. When cellular processes are perturbed and generation of free radicals overwhelms the antioxidants capacity of the neurons, a resulting redox damage leads to neuronal dysfunction and cell death. Cellular sources for production of redox-active molecules may include NADPH oxidases, mitochondria, cytochrome P450 and nitric oxide (NO)-generating enzymes, such as endothelial, neuronal and inducible NO synthases. Several neurodegenerative and developmental neurological conditions are associated with an imbalanced redox state as a result of neuroinflammatory processes and leading to nitrosative and oxidative stress. Ongoing research aims at understanding the causes and consequences of such imbalanced redox homeostasis and its role in neuronal dysfunction.

Keywords: nitrosative stress; nitric oxide; oxidative stress; neurological disorders; neurodegeneration; autism spectrum disorder; Alzheimer's disease; nitric oxide; redox signalling

Abbreviations:

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)
3-nitrotyrosination (3-NT)
adenosine triphosphate (ATP)
α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)
Alzheimer's disease (AD)
Antioxidant response element (ARE)
Autism spectrum disorder (ASD)
Bipolar disorder (BPD)
bone morphogenetic proteins (BMP)
catalases (CAT)
copper/zinc superoxide dismutase (SOD-1)
CREB binding protein (CBP)
dithiothreitol (DTT)
Dynamin-related protein 1 (Drp1)
endothelial NOS (eNOS)
glutathione peroxidases (GPx-1)

glutathione s-transferase (GST)
heme oxygenase 1 (HO-1)
Huntington's disease (HD)
HTT-associated protein-1 (HAP-1)
inducible NO synthase (iNOS)
long isoform of NOS1 adaptor protein (NOS1AP-L)
miniature inhibitory postsynaptic current (mIPSC)
medial nucleus of the trapezoid body (MNTB)
myocyte enhancer factor 2 (MEF2)
NADPH oxidase (Nox)
NADPH quinone oxido-reductase 1 (NQO-1)
neuroglobin (Ngb)
neuronal NO synthase (nNOS)
N-ethylmaleimide sensitive fusion protein (NSF)
nicotinamide adenine dinucleotide 2'-phosphate (NADPH)
N-methyl-D-aspartate (NMDA)
NO synthase (NOS)
nuclear factor erythroid 2-related factor 2 (Nrf2)
Parkinson's disease (PD)
post-synaptic density protein-95 (PSD-95)
protein kinase G (PKG)
reactive nitrogen species (RNS)
reactive oxygen species (ROS)
S-nitrosoglutathione (GSNO)
S-nitroso-glutathione reductase (GSNOR)
S-nitrosylation (SNO)
S-nitroso-*N*-acetylpenicillamine (SNAP)
Sodium nitroprusside (SNP)
soluble guanylyl cyclase (sGC)
superoxide dismutase (SOD)
thioredoxin (Trx)
thioredoxin reductase (TR)
Transient Receptors Vanilloid type 1 (TRPV1)
γ-aminobutyric acid (GABA)

1. Introduction

Brain function relies on a precise regulation of neuronal properties including synaptic release mechanisms of various neurotransmitters, activities of their corresponding post-synaptic receptors and neuronal excitabilities. Not only a fine-tuned control of excitatory *versus* inhibitory synaptic pathways is essential for a physiological functioning of the brain but also underlying regulation of ion channels within each neuron requires precise time- and space-

dependent adaptations and regulations of their activities [1]. In order to allow all of the above processes to work in a concerted and physiological manner, numerous regulatory neuronal signalling routes act together to provide the needed plasticity. As the brain is the main consumer of oxygen within the body, the inevitable production of reactive oxygen species (ROS) causes challenges for every active neuron. Neuronal activity itself produces several sources for redox stress with the main reactive molecules being nitric oxide (·NO) and associated reactive nitrogen species (RNS) as well as ROS [2, 3]. Controlling and inactivating the redox stress caused by these molecules possess a great challenge for neurons and once the antioxidant and scavenging capacity is overwhelmed, the neurons suffer oxidative damage which may result in neurological and degenerative conditions. Above signalling routes may impact on protein functions by NO-mediated post-translational modifications, such as protein S-nitrosylation (SNO), also referred to S-nitrosation, or 3-nitrotyrosination (3-NT). NO and associated redox-active intermediates many of which can oxidize, nitrosate or nitrate other molecules. The NO-derived reactive species are typically short-lived and include nitrogen dioxide ($^{\bullet}NO_2$), dinitrogen trioxide (N_2O_3), nitroxyl (HNO) and peroxynitrite ($ONOO^-$/ONOOH) and have unique reactivities, depending on the particular properties of each, they may lead to oxidation, nitrosation or nitration [4]. The formation of NO-derived oxidants is linked to the presence of oxygen species, as demonstrated by peroxynitrite formation as a result of the reaction of $NO^{\bullet}$ with the superoxide radical ($O_2^{\bullet-}$). All of the above compounds interact with a multitude of cellular signalling molecules and proteins in various tissues. These effects occur in the vasculature, where nitrergic signalling was first characterised [5, 6], during neuroinflammatory responses [7, 8], in neurovascular coupling [9, 10], the olfactory, auditory and nociceptive systems (see review [11]). This review focuses predominantly on neuronal aspects of NO signalling and redox biology in physiology and disease.

In light of more recent findings illustrating the impact of physiological oxygen levels on redox signalling, it is important to consider that studies summarised in this review were performed under distinctly different oxygen levels. As the generation of NO intermediates depends on the oxygen levels present, it is not surprising that under different oxygen tensions, nitrergic effects vary greatly or even contradict themselves. Most data from experiments in cell culture and brain slice preparations were generated under standard atmospheric high and unphysiological oxygen levels (~20% O_2/20kPa or 95% O_2/95kPa). On the other hand, *in vivo* studies were conducted under physiological oxygen tension which lies at around 4-5% O_2 (4-5kPa) within the brain. This discrepancy between the standard *in vitro* (hyperoxia) and *in vivo* conditions (normoxia) has been investigated and discussed in more recent studies and reviews [12, 13]. In particular, *in vivo* under physiological conditions, neurons are exposed to low oxygen levels at about 2-4kPa and comparisons between normoxia (*in vivo*-like 2-4kPa O_2) and hyperoxia (*in vitro*-like ~20kPa O_2) conditions in various cellular models revealed fundamental differences in redox signalling, mitochondrial phenotypes, protein expressions and NO bioavailability [14-18]. Likewise, it is important to consider conditions of redox signalling during neuronal development and stem cell research [19, 20]. All of the studies

discussed below have to interpreted in light of the redox conditions under which the experiments have been performed.

2. Redox signalling in neuronal function

The brain has a high-level metabolic activity and neuronal firing requires continuous oxygen supply to provide sufficient energy from mitochondrial respiration to maintain the ion homeostasis. This energy in form of adenosine triphosphate (ATP) is necessary to allow ATPases to maintain ions gradients across the cell membrane. However, mitochondrial activity also induces oxidative stress conditions mediated by oxygen free radicals. At the same time, neuronal activity leads to a calcium (Ca^{2+})-dependent production of NO *via* the activation of neuronal nitric oxide synthase (nNOS, NOS1) (Fig. 1). NO is a small, hydrophobic gaseous neurotransmitter that permeates membranes and interacts with molecular targets within a diffusion-limited space, providing physiological functions such as neuromodulation or neuro-vascular coupling [9, 21-24].

Several redox buffering and antioxidant systems are in place to provide a physiological redox homeostasis resembling an innate antioxidative defence system that includes various enzymatic and nonenzymatic antioxidants to neutralize or scavenge free radicals [25]. The main antioxidants systems within neurons include various endogenous enzymes with their substrates or coenzymes, along with exogenous antioxidant sources that maintain the redox equilibrium in cellular systems [26]. These include enzymes such as superoxide dismutases (SOD), catalases (CAT) and glutathione peroxidases (GPx-1). Endogenous antioxidant activity is directly regulated by the nuclear factor erythroid 2-related factor 2. It is a ubiquitous redox-sensitive transcription factor that stimulates the expression of antioxidant response element (ARE)-containing gene promoters involved in ROS detoxification. These promoters are responsible for expression of heme oxygenase 1 (HO-1), glutathione s-transferase (GST) and nicotinamide adenine dinucleotide 2'-phosphate (NADPH) quinone oxido-reductase 1 (NQO-1). In addition to the enzymatic antioxidant activities, low-molecular-weight nonenzymatic antioxidant molecules include thiol compounds (glutathione), uric acid and coenzyme Q10 (CoQ10) [27]. In addition to NO, other intracellular sources have been identified to generate physiologically relevant redox molecules. H_2O_2 is most notably produced within mitochondria through the dismutation of $O_2^{\bullet-}$ and outside the mitochondria by cytoplasmic oxidases and NADPH oxidase (Nox) [28]. H_2O_2 is the source of the hydroxyl radical ($^{\cdot}OH$), which readily crosses the cell membrane presenting a potential for further cellular redox stress. In addition to nitrergic regulation, a prominent role of H_2O_2 is known to contribute to redox signalling as a secondary messenger molecule and it has been implicated in regulating neuronal plasticity and transmitter release [29-31].

Both redox-active molecules, $^{\bullet}NO$ and $O_2^{\bullet-}$, are able to react to form additional intermediate reactive species and their abilities to modify proteins have been studied on the biochemical and functional level characterising specific NO- and redox-mediated mechanisms. NO can either, *via* activating the canonical soluble guanylyl cyclase (sGC)/cGMP-dependent pathway or *via* the generation of post-translational protein modifications impact on neuronal activity

and excitability (Fig. 1) [32, 33]. Application of NO-donors (10µM NOC-5, 100µM sodium nitroprusside [SNP], PapaNONOate, *S*-nitroso-*N*-acetylpenicillamine [SNAP], DEA-NONOate) modulates voltage-gated ion channels, such as the high voltage-gated potassium channels Kv3 and Kv2 in the medial nucleus of the trapezoid body (MNTB) in brain slice preparations, Kv3 channels expressed in cultured CHO cells [34-37] as well as the M-current (Kv7) in cultured trigeminal ganglia neurons [38]. These modifications are the result of either direct cGMP/protein kinase G (PKG)-mediated phosphorylation events or occur *via* cysteine S-nitrosylation and result in changes of neuronal excitabilities. Other ion channel targets include L-type calcium channels in principal neurons of the MNTB in brain slice preparations where NO application (as provided by perfusion with 100µM SNP-containing solution) induces an augmentation of currents requiring cGMP signalling [39].

Reportedly, ion channels which regulate hippocampal activities and are involved in learning and memory and dementia processes are affected by NO and redox signalling. Studies of the gating mode of the voltage-dependent Kv1.2 channel expressed in cultured mouse ltk- fibroblasts is affected by the redox environment with the inhibitory state of the channel being strongly favored in a reversible manner by mild reducing conditions (0.6mM dithiothreitol [DTT], [40]). Mutagenesis of candidate cysteine residues within the channel protein fails to abolish redox sensitivity and the authors suggest that an extrinsic, redox-sensitive binding partner imparts these properties. Further studies of nitrergic effects within the hippocampus revealed an nNOS-dependent modulation of Transient Receptors Vanilloid type 1 (TRPV1) channels in brain slices which implicates an activity-dependent regulation of this ion channel and thereby modifies excitation of CA1 pyramidal neurons [41].

Strong evidence for nitrergic regulation of neurotransmitters has been provided by earlier studies showing NO's inhibitory actions on N-methyl-D-aspartate (NMDA) receptors by S-nitrosylation at Cys399 on the NR2A subunit when expressed in *Xenopus* oocytes [42]. This mechanism was induced by S-nitrosocysteine (500µM) application and reversed by DTT (3mM). Other mechanisms of mitochondrial-derived ROS-mediated regulation of neuronal plasticity include an increase surface expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and NMDA receptors containing GluA1 and NR2B subunits (Fig. 2) [43].

Several main neurotransmitter signalling cascades are regulated by multiple redox pathways. γ-aminobutyric acid (GABA) release and GABA receptors can undergo modulation by ROS. GABAergic miniature inhibitory postsynaptic current (mIPSC) frequency was reduced in stellate cells of the mouse cerebellum in response to mitochondrial-derived ROS production following antimycin-A application which required the α3-containing $GABA_A$ receptors [44]. Conversely, it has been reported that 1mM H_2O_2 application enhances the release of GABA and glutamate in the ventral horn neurons of the rat spinal cord [30], a mechanism which required modulation of Ca^{2+} channels and Ca^{2+} release from intracellular stores. In addition, ROS can modulate both, the activity of phasic and tonic $GABA_A$ receptors as well as GABA release from presynaptic terminals (see review [45]). Indirect evidence suggests that Nox-1 derived ROS signalling is able to modulate NMDA receptors containing the NR1 subunit

(Cys744) thus contributing to depression-like behaviour in mouse [46]. More direct mutagenesis studies revealed that redox modulation of the three pairs of cysteine residues induce various kinetic alterations of NMDA receptor-mediated currents in *Xenopus* oocytes expressing NR1/NR2A receptors. These affected cysteines are Cys87 and Cys320 in NR2A which underlie a fast component, and Cys79 and Cys308 in NR1 which underlie an intermediate component, and Cys744 and Cys798 in NR1 which are responsible for a persistent effect on receptor currents [47]. The findings also illustrate that distinct cysteine residues are affected by ROS and RNS in a different manner highlighting a specificity of redox signalling. Although there are numerous cysteines present in most proteins, it has been found that there is a consensus motif of nucleophilic residues surrounding a critical cysteine that facilitates the formation of a thiolate anion and thus increases the susceptibility of the sulfhydryl to S-nitrosylation [48, 49] suggesting that only specific subsets of cysteine residues are susceptible to this type of post-translational modification.

NOS is distributed ubiquitously in the organism, and this determines the involvement of NO in a variety of physiological processes. NO cannot be stored in the cells and the its levels depend on new synthesis and degradation to execute its role in the regulation of biological processes [50]. Therefore, the physiological, as well as the pathological, effects of NO largely depend on the systemic, tissue and subcellular localization of NOS isoform. Bredt *et al.* were the first to demonstrate in 1990 that NOS in the brain is exclusively associated with particular populations of neurons [51], and this corresponds to differential effects of NO in the CNS. NO is synthesized by three isoforms, which have different localization and respectively, different functions. Neuronal (nNOS) is located mainly in central and peripheral neurons, where NO takes part in the regulation of neuronal communication such as through S-nitrosylation of NMDA receptors [52]. nNOS exists in both particulate and soluble forms in the brain and the differential distribution of this enzyme is associated with its diverse functions [50]. nNOS has also been found in the sympathetic ganglia, adrenal glands, spinal cord, epithelial cells of various organs, peripheral nitrergic nerves, kidneys, pancreatic islet cells and vascular smooth muscles [53]. Endothelial NOS (eNOS, NOS3) produces NO in the endothelial cells of blood vessels. NO produced by eNOS exerts vasodilation due to the relaxation of the smooth muscles of blood vessels [54]. This NOS isoform was also identified in platelets, some certain neurons and cardiac myocytes [53]. Both nNOS and eNOS are constitutively expressed, produce low levels of NO over long periods, and their activity depends on Ca^{2+} cycling [55]. Inducible NOS (iNOS, NOS2) is localized predominantly in glial and immune cells. This NOS isoform is Ca^{2+}-independent, produces high levels of NO for short periods and plays a protective role [56]. iNOS promotes pathogen killing and also produces immune-regulatory effects [57].

Subcellular localization of NOS is an important determinant of the biological effects of NO. It has been suggested that nNOS binds to the plasma membrane either directly or *via* adapter proteins [58]. For example, nNOS can be attached to the postsynaptic membrane by binding to the post-synaptic density protein-95 (PSD-95). It links nNOS to the NMDA receptor promoting the activation of nNOS [59]. nNOS can be linked to other adapter proteins, such as

SAP-90, syntrophin or postsynaptic density-93 (PSD-93) [60]. nNOS is also present in a soluble form in the cytoplasm of neurons. Rothe *et al.* have found that brain nNOS in rats was mainly distributed in the cytosol of neurons far from membranes [61]. Importantly, nNOS contains a protein interaction module, PDZ (post-synaptic density protein, discs-large, ZO-1) domain, which binds to the PDZ domains of other proteins [50]. These interactions often define the subcellular localization and functions of nNOS. For instance, it has been revealed that the protein CAPON binds to the N-terminal PDZ domain of nNOS by its C-terminal PDZ domain and a N-terminal phosphotyrosine binding (PTB) domain [62]. The interaction of nNOS and CAPON triggers a cascade of protein-protein interactions leading to iron uptake in neurons [50] which is an important cofactor in various biological and biochemical processes.

It has been established that NOS takes an active part in the regulation of mitochondrial functions [63]. Therefore, mitochondrial NO production and its role in mitochondria have attracted significant interest. Ghafourifar *et al.* first suggested the existence of constitutively active NOS in the mitochondria, referred to as mtNOS [64]. mtNOS is bound to the inner mitochondrial membrane facing the matrix, probably playing a role in the regulation of Ca^{2+} cycling [64]. It has been suggested that an increase in Ca^{2+} influx accelerates NO production by mtNOS, which in turn decreases oxygen consumption and alters the mitochondrial membrane potential. NO produced by mtNOS has also been shown to inhibit complex IV of the electron transport chain (*i.e.* cytochrome *c* oxidase) [65]. These effects of NO produced in the mitochondria are reversible and can be modified by opposing reactions [66]. In addition, NO stimulates the synthesis of new mitochondria *via* activation of the peroxisome proliferator-activated receptor gamma coactivator-1 (PGC-1) [67]. Thus, NO produced in mitochondria is an important regulator of different biological processes in physiological conditions. Unfortunately, despite the intensive studies that have been performed, the identity of mtNOS remains uncertain.

3. Nitric oxide and redox signalling in the developing brain

NO is a major contributor to essential inter- and intra-neuronal signalling involved in neurogenesis and neurodevelopment [68]. Several previous studies have the involvement of NO in neuronal development shown under *in vivo* conditions where inhibition of nNOS, either by genetic knockout (KO) or by pharmacological agents (L-NAME [90 mg/kg per day for 15 days; 7-nitroindazole [7-NI, 30 mg/kg for 4 days] in mice or L-NAME [120 mg/kg for 7 days] in rats) positively impacts on neurogenesis [69-71] implicating a physiological role of NO as a negative regulator of neurogenesis. Based on these observations, it is not surprising that NO and redox dysregulation during neurogenesis may result in major developmental and psychological disorders.

The myocyte enhancer factor 2 (MEF2) is a transcription factor that promotes neurogenesis during early development and S-nitrosylation at Cys39 causes MEF2 to exhibit reduced binding affinity to DNA which ultimately inhibits its transcriptional activity [72]. Consequently, SNO-MEF2 lowers the expression levels of orphan nuclear receptor tailless [73] - a regulator of adult neurogenesis that contributes to memory and learning processes [74]. Work by

Lipton and colleagues reported high levels of SNO-MEF2 in AD patients which contributes to neurodegeneration. The reported changes were seen both in human post-mortem brains and in mutant transgenic mouse brains [73]. Studies on nNOS gene deletion models in mice showed atypical hippocampal dendritic branching [75] and reduced neurogenesis [69] implying that NO plays an essential key role in neurodevelopment. In early studies, it has also been shown that the activity of nNOS, but not the inducible or endothelial isoforms of NOS, is required to support the survival of a proportion of cerebellar Purkinje neurons *in vitro*, whereas high concentrations of exogenous NO reduces Purkinje neuron survival in culture [76]. This confirmed that low levels of endogenous NO, released by nNOS, are beneficial to cerebellar Purkinje neuronal development, whereas high levels of nitrosative stress (induced by exogenous donor application: >200μM NOC-18, 100μM GSNO, 100μM SIN-1) are detrimental to both the survival and ability to form synaptic connections of E19 cerebellar Purkinje neurons during 6 days *in vitro* culture [76]. There is evidence that overexpression of the long isoform of NOS1 adaptor protein (NOS1AP-L), a protein implicated in schizophrenia [77], resulted in a decreased branching of cultured rat hippocampal neurons [78] and mouse hippocampal and cortical neurons [79], and also affects radial migration of cortical neurons [80]. NOS1AP is a binding partner of nNOS [81] and competes with PSD-95 for nNOS binding which presumably reduces NMDA receptor signalling *via* PSD-95 and nNOS interactions thereby altering endogenous NO release.

Persistently increased levels of ROS are associated with the development of several neurodegenerative diseases [82-84] but a growing body of literature has started implicating positive effects of ROS signalling in neurogenesis. Redox-mediated effects on neuronal development include Nox-2 activity which, when inhibited either pharmacologically or by siRNA, decreases bone morphogenetic proteins (BMP)-induced dendritic growth of cultured rat sympathetic neurons [85] implicating a ROS requirement for neuronal growth. This finding has been substantiated by a study showing that lowering cytoplasmic levels of reactive oxygen species with a free radical scavenger, N-tert-butyl-α-phenylnitrone, or by inhibiting specific sources of reactive oxygen species, such as Nox or lipoxygenases, reduced the F-actin content in the peripheral domain of growth cones of *Aplysia* bag cell neurons [86]. There is growing evidence to support a role for ROS in neurogenesis, and data suggests that endogenous ROS levels fluctuate throughout differentiation to drive different phases during development. In fact, neuronal stem cells cultured through the neurosphere assay, a culture method to clonally amplify neuronal stem cells [87], ROS generated by addition of 2-4μM exogenous H_2O_2 to the culture media induced a stimulatory effect on stem cell growth [88] and even, application of 50μM SIN-1 for 6 days in culture, promotes cell survival of proliferating mouse embryonic hippocampal-derived neural progenitor cells [89]. Cells may produce different levels of ROS under physiological conditions depending on their developmental stage [90], and thus respond differently throughout development to oxidative stress.

Taken together, these studies show that redox signalling seems crucial during early

development and a dysregulation of signalling pathways may lead to various neurodevelopmental diseases.

4. Multiple redox stress pathways in neurodegeneration

Neuroinflammatory signalling during and prior to the onset of neurodegenerative conditions resembles a major source of NO, produced by the inducible NOS (iNOS) isoform following activation of microglia. The resulting high levels of NO and other redox-active molecules produced during prolonged periods of neuroinflammatory activity may further aggravate neurological and neurodegenerative disorders [91, 92]. Numerous target molecules have been identified which are directly modified by aberrant NO-mediated post-translational modifications in major neurodegenerative and protein-misfolding conditions such as AD and Parkinson's disease (PD) [92, 93] as discussed in several review articles [94-100].

SNO protein modifications may induce further protein misfolding, neuronal and synaptic damage, disturbed mitochondrial function and apoptosis. Importantly, these modifications are reversible, and the reversibility depends greatly on the presence of antioxidants such as glutathione and the activities of de- and trans-nitrosylases [101, 102]. De-nitrosylation can attenuate the effects of excessive NO generation and ameliorate nitrosative stress including several identified de-nitrosylases such as the thioredoxin (Trx)/thioredoxin reductase (TR) system, glutaredoxin (Grx)/glutathione reductase (GR) system, thioredoxin-related protein 14 and the GSH/GR system [103-105]. The effect of this de-nitrosylating process has been shown to reverse Dynamin-related protein 1 (Drp1) S-nitrosylation which reduces neuronal apoptosis following subarachnoid hemorrhage both *in vivo* and *in vitro* [106]. In order to identify the proteome affected by NO, work by Amal and colleagues used the SNOTRAP tool to characterize SNO modifications and their physiological functions in different brain regions [107] and during aging [108] and in both genders in mouse [109].

Additional nitrergic stress conditions are mediated by increased levels of 3-NT which have been reported in neurodegenerative conditions [110]. In a PD model, modified proteins include α-synuclein resulting in the formation of aggregates [111] and α-tubulin which results in reduced mitochondrial transport [112]. In AD patients, 3-NT formation of Aβ is thought to further facilitate its aggregation, thereby contributing to the pathology [113].

In addition to ROS and RNS species, divalent redox metal homeostasis plays an important role in determining the redox status of a cell. Reports show that many redox metals are abnormally regulated in several neurodegenerative diseases. One of the major redox metals is iron and iron dys-regulation, also referred to as ferroptosis, plays a major role in several neurodegenerative disorders [114]. The homeostasis of iron and other divalent redox metals is controlled by the interplay between various influx and efflux processes and the adequate use of intracellular storage. Any dysfunction of these regulatory mechanisms will lead to an imbalance and further disturbance of the physiological redox state. Studies have reported increases in iron levels in the central nervous system in AD patients [115] which, in addition to zinc ions, can induce aggregation of amyloid β (Aβ) *in vitro* [116] as well as deposition of

Aβ in mouse models of AD. Reduced levels of zinc have been shown in serum of AD patients and the decreased zinc levels are associated with elevation of brain Aβ deposition [117]. Increased iron levels in the substantia nigra pars compacta on the other hand have been detected in PD patients [118], including various familial forms, and evidence for an altered redox metal homeostasis, including changes in zinc, iron and manganese ions, has been reported in prion diseases in human and mouse models [119, 120]. The disturbed redox metal homeostasis maybe associated with NO-mediated S-nitrosylation events of the divalent metal transporter 1 which results in a change in intracellular ion concentrations, such as cytosolic iron [121] thereby creating a feedback loop to induce further redox stress in conjunction with an increase of ROS and RNS.

Based on the evidence that aberrant S-nitrosylation and 3-nitrotysosine contribute to neurodegeneration, it has been suggested that targeting and reversing NO-mediated posttranslational modifications can alleviate pathology [91]. This approach involves the inhibition of NOS activity [122-124] to suppress overall NO production, but more importantly, recent drug discovery efforts have identified small-molecule inhibitors of the enzyme responsible for reversing S-nitrosylation, S-nitroso-glutathione reductase (GSNOR) [125]. Among these inhibitors, N6022 binds to the enzyme substrate-binding pocket, thus serving as a selective inhibitor of GSNOR [126]. By inhibiting GSNOR, this drug enhances GSNO levels and the intracellular SNO-protein pool which potentiates physiological NO availability. An additional approach to regulate protein de-nitrosylation identified thioredoxin-mimetic peptides that catalyze the reduction of SNO, protecting cells from nitrosative stress [127].

The widely expressed glutamatergic neurotransmitter receptor, the NMDA receptor, is modulated by redox and NO signaling. Data suggest that homocysteine (HCY), an endogenous redox active amino acid, induced native NMDAR currents in neurons mediated by the "synaptic-like" GluN1/2A NMDA receptor subunits [128]. This implies that in hyperhomocysteinemia, a disorder with high plasma level of HCY, HCY may persistently contribute to post-synaptic responses mediated by GluN2A-containing NMDA receptors. NMDA receptors were identified as SNO targets by Lipton and colleagues showing the inhibitory actions of S-nitrosylation of NMDA receptors at Cys399 at the NR2A subunit [42, 129], an effect deemed to be neuroprotective by curtailing excessive calcium entry in disease-link excitotoxicity. Moreover, mitochondria-derived ROS promote NMDA receptor-containing GluA1 and NR2B subunit surface expression leading to calcium overload and excitotoxicity in a model of frontotemporal dementia [43].

Along with nitrosative stress, nitrative stress contributes significantly to the pathology of neurodegenerative diseases. Nitrative stress represents a condition under which RNS levels significantly overwhelm the capability of the mechanisms of RNS detoxification in a biological system. It is manifested in the nitration of biomolecules, resulting in cell damage [130]. Nitrative stress is inextricably linked to oxidative stress. These forms of stress are

characterized by elevated levels of RNS and ROS, molecules like hydrogen peroxide (H_2O_2), superoxide ($O_2^{\bullet-}$), hydroxyl radical ($^{\bullet}OH$), peroxynitrite ($ONOO^-$) or nitrogen dioxide ($^{\bullet}NO_2$) [131, 132]. Oxidative/nitrative stress can be the result of the excessive production and the insufficient removal of ROS and RNS by the antioxidant and NO inactivation mechanisms [131]. NO can interact with $O_2^{\bullet-}$ and form $ONOO^-$ [133], a highly reactive molecule. Notably, excessive formation of $ONOO^-$ in mitochondria promotes cytochrome *c* release [134]. The release of cytochrome *c* from the mitochondria is known to trigger apoptosis by activation of the caspase cascade [135, 136]. $ONOO^-$ can also halt the functioning of the electron transport chain by competing with molecular oxygen [137]. Several biochemical processes can form $^{\bullet}NO_2$, including NO autoxidation and $ONOO^-$-catalyzed reactions [138]. $ONOO^-$ or $^{\bullet}NO_2$ nitrate other molecules, *e.g.* aromatic and aliphatic residues of proteins or aliphatic chains of fatty acids [139]. Tyrosine residues are the main target for the nitration of proteins leading to the formation of 3-NT [140], the post-translational protein modification (PTM) that may affect the properties of the protein. Nitration of tyrosine impairs its hydrogen binding ability, which leads to abnormal changes in the protein structure [141, 142]. This PTM interferes with tyrosine phosphorylation and thus affects cellular signaling [110] as seen in a variety of brain disorders. Thus, Increased levels of 3-NT were found in patients with neurodegenerative diseases, such as AD [143], PD [144], Huntington's disease (HD) [145] and neurodevelopmental disorders, such as autism spectrum disorder (ASD) [146].

While the mechanisms of removal of ROS by the cellular antioxidant systems have been well-investigated (see [147] for review), the NO inactivation mechanisms remain obscure [139]. One of the suggested mechanisms is oxygen-dependent NO inactivation. Even though the direct reaction between NO and O_2 is slow, the pool of these molecules in the hydrophobic layer of cell membranes considerably accelerates the NO consumption [148]. NO can directly interact with transition metals, in particular the iron of hemeproteins. It has been shown long ago that in the mitochondria, NO binds to cytochrome *c* oxidase (CcO) inhibiting the activity of this enzyme [149]. NO dissociation returns CcO to a fully active state [150]. This inhibition mechanism is supported by high O_2 concentration and contributes to the regulation of NO concentration in the tissue [151]. Other heme-containing enzymes, including prostaglandin H synthase, lipoxygenases, cycloxygenase-1 [152-154] and peroxidases [155] can catalyze redox reactions and inactivate NO. The globin family proteins, such as neuroglobin (Ngb), hemoglobin and cytoglobin, may also inactivate NO in the brain [156, 157]. It has been suggested that Ngb plays NO scavenging role and its overexpression protects the brain against ischemia-induced NO cytotoxicity [158]. Hemoglobin is considered the major NO scavenger in circulation, due to its high concentration in erythrocytes and its ability to readily react with NO. However, intravascular flow can reduce the efficacy of NO scavenging by hemoglobin by 3-4 orders of magnitude [159].

Thus, the excessive production of ROS and RNS, on the one hand, and the reduced capability to neutralize or remove these harmful molecules, on the other hand, lead to brain injury,

pathological changes in the protein functions, and signal transduction affecting a variety of physiological processes in the brain.

A variety of redox-active molecules, including NO and RNS, cause modifications in many biomolecules, which represent an integral part of various pathological processes [160]. Growing evidence is accumulating on the involvement of free radical NO and its intermediates in the pathogenesis of neurodegenerative diseases. Nowadays, it is not known whether NO is a cause or consequence of neurodegeneration. Nevertheless, numerous reports suggest that its functions depend on its cellular level. If the production of NO crosses a threshold, it could initiate pathological reactions [161]. Below, we summarized evidence of NO contribution to the main neurodegenerative diseases.

4.1. Alzheimer's disease

AD is characterized by two key features, extracellular aggregates of Aβ forming the neuritic plaques and intracellular neurofibrillary tangles caused by the excessive phosphorylation of tau protein [162]. It has been found that Aβ fibrils can exert a toxic effect by stimulating ROS production, including $ONOO^-$ [163]. Chronic $A\beta_{1-40}$ intracerebroventricular infusion has been shown to induce $ONOO^-$ formation followed by 3-nitrotyrosination of proteins [164]. nNOS-positive reactive astrocytes were identified in AD patients near amyloid plaques colocalized with neuron loss [165]. It has also been found that particular cerebral regions of AD patients have higher 3-NT levels of proteins, specifically in the hippocampus and the cerebral cortex [166, 167]. Other proteins 3-nitrotyrosinated in AD are associated with glucose metabolism (triosephosphate isomerase, γ-enolase/α-enolase and lactate dehydrogenase) [168]. Post-mortem studies on AD-afflicted human brains demonstrated dramatically increased levels of nitration of neurofibrillary tangles in the hippocampus [166]. Numerous proteins associated with synaptic function and neuronal survival are abnormally S-nitrosylated in AD, resulting in synaptic loss and neurodegeneration [169]. A post-mortem study performed by Horiguchi *et al*. have found that nitrated tau protein is widespread in brains of AD patients [170] pointing towards the involvement of aberrant NO signalling in AD pathogenesis.

4.2. Parkinson's disease

PD is a neurodegenerative disorder characterized by a progressive loss of dopaminergic neurons in the substantia nigra, leading to the dysfunction of extrapyramidal motor neurons, bradykinesia, rigidity and tremor [171].

Post-mortem examinations have revealed oxidative damage in PD patients [172] and elevated 3-NT levels in the degenerating neurons of substantia nigra [173]. Results of several studies imply that $ONOO^-$ contributes to the pathogenesis of PD [174]. Endogenous NO has been shown to promote dopamine efflux in the striatum *via* the increase in the glutamatergic tone [175]. However, high levels of NO exert the opposite effect on NMDA receptor-mediated dopamine release. This effect might be explained by the triggering of a negative feedback mechanism or augmented GABA release [176]. *In vitro* studies have found that S-nitrosylation

of parkin, a protein that adds ubiquitin on specific substrates, reduces its protective effect [177] leading to the accumulation of neurotoxic proteins and promoting ER stress [178]. The involvement of NO in PD was confirmed by studies on nNOS knockout mice. The transgenic mice were more resistant to neurotoxicity induced by an inducer of PD, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [179]. Furthermore, it has been revealed that polymorphonuclear cells isolated from PD patients are characterized by increased production rates of NO (~30% increased rate), accumulation of the 3-nitrotyrosinated proteins and a neuronal upregulation of nNOS [180]. Also, an overexpression of nNOS protein was found in basal ganglia and circulating neutrophils of patients with PD. Interestingly, glial derived neural factor (GDNF) which induces a protective effect in PD [181], inhibits activity of nNOS and reduces apoptosis in neurons [65]. These observations convincingly provide evidence that NO and its intermediates significantly contribute to the pathogenesis of PD.

4.3. Huntington's disease

HD is a condition causing dementia and involuntary movements accompanied by the loss of neurons in specific brain regions, predominantly in the striatum [182]. HD is caused by an expansion of a CAG trinucleotide repeat on the huntingtin (*HTT*) gene situated on the short arm of chromosome 4 [183]. In HD patients, mutant *HTT* triggers neurotoxicity *via* activation of NMDAR [184], lack of transcriptional effects and aberrant vesicle trafficking [185]. Two pathways have been proposed to link HD with NO production. One is htt/HAP-1 (HTT-associated protein-1)/calmodulin/NOS and another route is *via* CREB binding protein (CBP)/HTT/NOS following HAP-1 interaction with HTT [186], the resulting HAP-1/HTT complex can bind to calmodulin which regulates the activity of nNOS and eNOS [187]. HTT can also interact with CBP and inhibit nNOS transcription [188]. Furthermore, the activity of CREB/CBP complex is regulated by the calmodulin kinases [189] which can be inhibited by the interaction of calmodulin with HTT/HAP-1 complex. These data are consistent with the increased expression of iNOS observed in vascular, glial and neuronal cells isolated from the brains of HD patients and HD mouse models [190]. The increased levels of RNS and oxidative stress have been observed in HD patients and HD transgenic mice has been reported [191, 192].

4.4. Amyotrophic lateral sclerosis

ALS is characterized by the progressive loss of motor neurons that control voluntary muscles [193]. The death of motor neurons is caused by caspases 1- and 3-induced apoptosis [194, 195]. It has been established that NO-dependent glutamate neurotoxicity is implicated in pathogenesis of sporadic ALS [196, 197]. Studies have shown that apoptosis of motor neurons in ALS is associated with 3-nitrotyrosination of proteins [198] and the irreversible inhibition of the electron transport chain in the mitochondria of these cells [199]. Treatment with a non-selective NOS inhibitor L-NAME reduced the motor neuron death in an G37R or G85R mutant mice (models of ALS) [200], confirming the involvement of the abnormal levels of NO ALS pathology. Consistent with these data, increased levels of NO metabolite levels in the cerebrospinal fluid of ALS patients have been confirmed [201]. Other research suggest that

astrocytes are the major source of NO in ALS. They might be involved in the pathogenesis of this disease by the production of molecules such as nerve growth factor and Fas-ligand [202] which activate nNOS, p38 MAPK and caspases 3 and 8 [203]. Twenty percent of familial ALS is related to gain-of-function mutations in the enzyme copper/zinc superoxide dismutase (SOD-1) [204]. The superoxide binding site of the mutant SOD-1 is easily accessible to other oxidants like H_2O_2 and $ONOO^-$ [205]. This may cause a loss of affinity for zinc in the mutant enzyme [206]. The reaction of $ONOO^-$ with mutant SOD-1 allows the formation of RNS and trigger of apoptosis [207]. Taken together, data are supporting the notion of high levels of NO and its related species play a key role in ASL pathology.

5. The role of NO in neurodevelopmental disorders: focus on autism spectrum disorder

In addition to aberrant redox signalling in several neurodegenerative disease, forms of neurological disorders are also impacted on by dys-regulated NO signalling. ASD is a neurodevelopmental disorder associated with deficits in communication and social skills, and repetitive behaviours [208]. ASD can be caused by both genetic mutations and non-genetic (environmental) factors [209]. As of today, there is no cure for ASD and some symptoms can be treated by prescription psychiatric medications and the World Health Organization indicates that between 1-1.5% of children suffer from ASD worldwide [210, 211]. Early clinical studies suggest that the levels of NO and cytokines involved in NO production, might be high in children suffering from autism [212, 213] and one study proposed the use of NO metabolites (NO_X) as biomarker for ASD as urinary levels of NO_X were elevated in children with ASD [214].

To address this questions specifically, Amal and colleagues have studied the effects of SNO on mitochondrial functions in the Shank3 KO mouse model of ASD [215]. A mutation in the Shank3 protein results in its dysfunction which is among the most auspicious ASD-associated gene mutations [216]. Shank3 KO mouse models show alterations in biochemical, electrophysiological and other cellular pathways [217-219]. A study by Amal *et al*. was the first to report the direct alterations of NO signalling in the development of ASD [220]. The authors hypothesized that the Shank3 mutation leads to an increased Ca^{2+} influx that in turn promotes nNOS activity; this chain of events causes the increased NO formation and NO-related molecular changes, as reflected in elevations of cellular S-nitroso-glutathione (GSNO), 3-NT and SNO levels [220]. In Shank3 mutant mice, the SNO-proteome is reprogrammed, and several proteins may become dysregulated by aberrant S-nitrosylation or aberrant de-nitrosylation [220]. System biology analysis of cortices from wild type (WT) and Shank3 KO mice revealed a 9-fold change in the SNO level of proteins that are involved in the synaptic vesicle cycle (*i.e*., syntaxin-1a, synaptotagmin 1 and N-ethylmaleimide sensitive fusion protein (NSF)). The analysis also revealed enriched SNO proteins involved in synaptic vesicle cycle and oxidative phosphorylation in Shank3 KO mice. Gene ontology and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses of 6-week-old KO mice showed enhanced levels of several proteins that are known to play a role in neurodevelopment and ASD. The results of this study show a striking association between the mutated S*hank3* gene and NO [220].

Further, it was shown through protein-protein interaction analysis that the cortex of KO mice had a network of S-nitrosylated proteins functionally involved in the synaptic vesicle cycle, neurotransmission (protein phosphatase catalytic subunit α-Ppp3ca, syntaxin-1a, vesicle associated membrane protein 3 and others), and in the glutamatergic pathway (glutamate dehydrogenase 1, metabotropic glutamate receptor (mGluR), G-protein subunit α O1 Gnao-1 and others) [220]. An analysis comparing the shared SNO-modified proteins in the cortices of 6-week-old and 4-month-old KO mice showed enriched processes that are concurrently known for their involvement in ASD, such as the synaptic vesicle cycle. The interactome analysis of the shared SNO-modified proteins revealed protein clusters involved in the synaptic vesicle cycle (syntaxin-1a, Ppp3ca, NSF and Dnm1) and in glutamate regulation (glutamic-oxaloacetic transaminase-Got1, Got2, Gnao-1). The study also reported that calcineurin in the cortex was S-nitrosylated, which inhibits its phosphatase activity and increases the levels of phosphorylated Synapsin-1 and p-CREB proteins [220] which has also been reported in a different model of ASD [221]. The synaptic protein Synapsin-1 regulates vesicle exocytosis which is increased in response to its phosphorylation [222]. SNO of syntaxin-1a promotes formation of the complex SNARE and ultimately increases synaptic vesicle docking and fusion [223]. The finding of elevated levels of phospho-synapsin-1 in the cortex of mutant mice may suggest that SNO formation of calcineurin is responsible for increased vesicle mobilization and enhanced excitatory synaptic transmission. Elevated levels of SNO modifications of the mGluR7 was also detected in the cortex of Shank3 KO mice which suggests that S-nitrosylation of mGluR7 may lead to greater Ca^{2+} influx in presynaptic neurons and increased vesicle fusion [220]. The insights obtained from the *Shank3* mutation study are likely to be applicable to a broader group of patients with genetically diverse but mechanistically related etiology, and thus they may imply NO as an important pathological factor in ASD.

6. The role of NO in Schizophrenia and other psychiatric disorders

Schizophrenia is a severe, chronic and debilitating mental disorder that affects thinking, feelings and behaviours with aapproximately 1% of people suffer from Schizophrenia [224]. A precise cause disease has not been identified but the disorder is considered to be multifactorial [225]. Schizophrenia symptoms are divided into three categories: positive symptoms, negative symptoms and cognitive disturbances [225, 226]. Hallucinations, catatonic behaviour, delusions, and disturbed thought process are positive symptoms. Avolition, anhedonia and social withdrawal are negative symptoms [224]. NO has been suggested to play a role in the onset of schizophrenia [227, 228] and research indicates that impairments of dopaminergic and cholinergic pathways may be partly responsible for the progression of schizophrenia through NMDA receptor-dependent dys-regulation of NO signalling [229-231]. Additionally, polymorphism of the nNOS gene is a high-risk factor of schizophrenia development [232]. Additionally, altered NO metabolite levels, such as nitrite and nitrate, were also identified in schizophrenia and found to be reduced in plasma, serum and cerebrospinal fluid of schizophrenic patients [233-235]. When treated with the NO donor

sodium nitroprusside, schizophrenic patients had improved attention, cognition and working memory [236, 237] suggesting that NO deficiency plays a notable role in the pathology of schizophrenia.

Bipolar disorder (BPD), also referred to as manic depressive illness, is a chronic mental disorder [238]. Accurate and early diagnosis of BPD is difficult, however it is estimated that about 1% of people suffer from BPD [239]. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [240] divides BPD into four categories: bipolar I disorder, bipolar II disorder, cyclothymia and residual category [238]. These conditions are diagnosed based on the severity and duration of the manic and the depressive episodes. Defects in dopaminergic and serotonergic pathways are putatively responsible for the development of BPD [238, 241]. Of note, the role of NO signalling in BPD has been reported as a potential contributor. NOS activity was discernibly reduced in blood platelets of BPD patients as compared to healthy subjects as measured by L-citrulline production without presenting altered iNOS or eNOS protein levels which also translates into reduced cGMP levels [242]. Another study has shown that prescription lithium treatment increases the plasma levels of NO_X in BPD patients, indicating a role of lithium in regulation of NO signalling during depressive episodes [243]. However, the same study also found that basal plasma NO_X levels in BPD were not different compared to healthy controls. Conversely, other work did identify differences, namely that NO_X plasma levels were significantly higher in BPD patients compared to healthy controls [244, 245]. Andreazza *et al*. has confirmed an increased activity of NO signalling in patients with BPD through a meta-analysis [246]. The controversy of these data can be explained by the differences in both the stage or categories of the disorder and a plethora of medications and treatments that were not stopped for the different studies [243]. Nevertheless, the accumulated data can veritably show the involvement of NO in Bipolar disorders, although its mechanistic role awaits for further investigation.

7. Conclusion and future perspectives

Neuronal redox chemistry comprises of a multitude of signalling steps and molecules. The major redox-active species reside from oxygen and nitrogen free radicals as a product of cellular oxidative metabolism and enzymatic activities, including various NOS isoforms, in particular neuroinflammation-associated iNOS. The generation of $O_2^{\bullet-}$ within the mitochondrial matrix depends critically on the NADH/NAD^+ and coenzyme Q (CoQ)H_2/CoQ ratios and the local O_2 concentration, which are all highly variable and difficult to measure *in vivo*. Equally, the *in vivo* levels of NO are hard to quantify leaving us with the option to measure metabolites and secondary markers as readouts for the levels of reactive species. Due to the high diffusibility of the molecules and their metabolites, it is not surprising that their actions are broad and wide. Their activities determine physiological regulation of neuronal function and once a balanced redox equilibrium is compromised, such as under neurodegenerative and neurological conditions, cytotoxicity and dys-regulation of neuronal functions are the consequences. Importantly, the interpretation of some data is further confounded by the fact that studies have been performed under different O_2 concentrations

(*in vitro versus in vivo*) with many *in vitro* studies being conducted under unphysiologically high O_2 tension (at ~20kPa). The future challenge remains to identify the earliest signs and biomarkers of redox stress such as neuroinflammation and mitochondrial dysfunction in order to intervene with pathology and prevent further neuronal damage.

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Conflict of Interests

The authors declare no conflict of interest.

Figure Legends

Figure 1: Nitric oxide signaling cascades in physiology and pathology. A major source for NO generation is the result of microglial activation associated with iNOS upregulation. Concurrent neuroinflammatory signalling may cause mitochondrial dysfunction with both events contributing to ROS production. The oxygen free radical may react with $^{\bullet}NO$ to produce peroxynitrite ($ONOO^{-}$). Increased Ca^{2+}-dependent activation of postsynaptic nNOS, a consequence of aberrant NMDA receptor activity or induced by mutant protein interactions involved in NMDA receptor function (*i.e.* Shank) generates additional NO. The resulting elevated levels of NO and $ONOO^{-}$ generate further RNS and protein modifications like S-nitrosylation (SNO) and 3-NT. SNO formation is reversible and controlled by activities of de- and tans-nitrosylases in which the GSH/GSNO cascade plays a major role in de-nitrosylating high molecular weight proteins. GSH is generated by glutamate-cysteine-ligase (GCL) and GSNO further metabolized by GSNOR (GSNO Reductase) which produces oxidized GSH (glutathione disulfide; GSSG) which is converted into reduced GSH *via* activities of glutaredoxins (GRX). 3-NT formation is irreversible and requires the reaction of tyrosine residues with peroxynitrite ($ONOO^{-}$) which is generated by NO in the presence of excessive amounts of oxygen free radicals ($O_2^{\bullet -}$). Disease-associated increased amounts of $O_2^{\bullet -}$ may result from aberrant NADPH oxidase activities as a consequence of mitochondrial dysfunction.

Figure 2: Multifaceted functions of neuronal NO signalling. NO acts on multiple sides within neurons, pre- and post-synaptically, to modulate ion channels, neurotransmitter release and receptor function (active zone proteins, NMDAR, GABAR, AMPAR and associated proteins PSD-95, Stargazin, Gephyrin) and intracellular proteins either *via* the canonical cGMP/sGC pathway or by mediating post-translational protein modifications. Ion channels may be phosphorylated by protein kinase G (PKG) or modulated directly by cGMP binding (cyclic nucleotide-gated channels [CNG]). S-nitrosylation modifies proteins in a reversible fashion, 3-NT modifications remain permanent. The consequence of physiological NO signalling may be

required for plasticity and development and results in changes of neuronal excitability and firing activities; however, neuropathological and aberrant NO production may compromise protein function and thus further contribute to disease pathologies.

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