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Review

Functions and dysfunctions of nitric oxide in brain☆

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ABSTRACT

Nitric oxide (NO) works as a retrograde neurotransmitter in synapses, allows the brain blood flow and also has important roles in intracellular signaling in neurons from the regulation of the neuronal metabolic status to the dendritic spine growth. Moreover NO is able to perform post-translational modifications in proteins by the S-nitrosylation of the thiol amino acids, which is a physiological mechanism to regulate protein function. On the other hand, during aging and pathological processes the behavior of NO can turn harmful when reacts with superoxide anion to form peroxynitrite. This gaseous compound can diffuse easily throughout the neuronal membranes damaging lipid, proteins and nucleic acids. In the case of proteins, peroxynitrite reacts mostly with the phenolic ring of the tyrosines forming nitro-tyrosines that affects dramatically to the physiological functions of the proteins. Protein nitrotyrosination is an irreversible process that also yields to the accumulation of the modified proteins contributing to the onset and progression of neurodegenerative processes such as Alzheimer's disease or Parkinson's disease.

1. Introduction

Since the 19th century, nitrates and nitrites were known to be vasoactive, being applied in medicine however the mechanisms activated by such compounds were unknown [1]. At the beginning of the 80's of the last century the effect of endothelial cells in vasodilatation was demonstrated by stimulation with acetylcholine (ACh) [2] and later the endothelial-derived relaxing factor (EDRF) was identified as Nitric Oxide (NO) [3,4]. At the same decade the production of NO in cerebellar glutamatergic neurons was demonstrated after activation of *N*-methyl-D-aspartate receptor (NMDAR) [5]. From that time to the present a deep knowledge on the physiological and pathological roles of NO has been unveiled.

NO has pleiotropic effects in the different tissues of the body, and even it is present in plants, sharing similar production systems and signaling with animals [6]. In this review we will focus on the effects that NO carries out in brain.

2. Nitric oxide

NO is a gaseous molecule that can diffuse easily to the surrounding tissue. It is mostly synthesized by an enzymatic activity carried out by the family of NO synthases (NOS), which oxidize L-arginine (L-Arg) to yield citrulline and NO. Neurons, glia and vascular cells can express NOS and are potential sources of NO in brain [7]. L-Arg is a semi essential amino acid and it is not a limiting factor in NO production under physiological conditions since it can be produced from citrulline or glutamic acid, however a depletion of L-Arg can occurs when iNOS is active for long periods and therefore iNOS produces superoxide anion ($O_2\cdot^-$).

Abbreviations: ACh, acetylcholine; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; Aβ, amyloid β-peptide; Ca^{2+}, calcium; cGMP, cyclic GMP; CREB, cAMP-response element binding-protein; CSF, cerebrospinal fluid; eIF2α, eukaryotic initiation factor 2-α; eNOS, endothelial nitric oxide synthase; FAD, familiar AD; FMN, flavin adenine mononucleotide; GC, guanylyl cyclase; GSH, reduced glutathione; H_2O_2, hydrogen peroxide; HRI, heme-regulated eukaryotic initiation factor(eIF)2α kinase; HD, Huntington's disease; iNOS, inducible nitric oxide synthase; LBD, Lewy body disease; LTP, long term potentiation; MS, multiple sclerosis; $\cdot NO_2$, nitrogen dioxide; NADPH, nicotinamide adenine dinucleotide phosphate; NMDAR, *N*-methyl-D-aspartate receptor; nNOS, neuronal nitric oxide synthase; NO, Nitric oxide; NOS, NO synthase; NOX, NADPH oxidase; O_2, oxygen; $O_2\cdot^-$, superoxide anion; OH·, hydroxyl radical; ONOO-, peroxynitrite anion; PD, Parkinson's disease; PS1, presenilin 1; PS2, presenilin 2; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, superoxide dismutase; TPI, triosephosphate isomerase; Trx, thioredoxins; VGCCs, voltage-gated Ca^{+2} channels; VSMC, vascular smooth muscle cells

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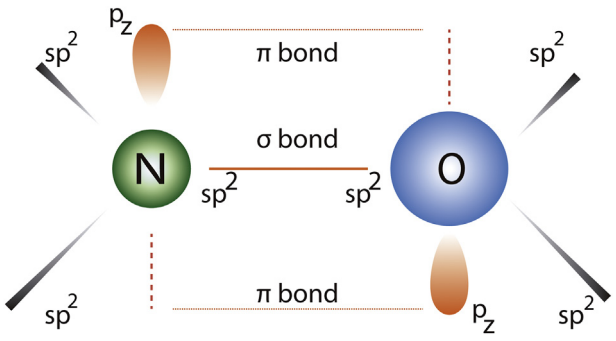

Fig. 1. NO molecule. Oxygen and nitrogen has a double covalent bond. The nitrogen atom lacks of one electron in its sp2 orbital, which makes NO a high reactive molecule.

NO is produced mainly by NOS, but there are other alternative sources of NO such as the non-enzymatic oxidation of L-Arg [8], xanthine oxidase [9] and others reductases able to transform nitrates into nitrites that will finally produce NO [10,11]. The generation of nitrates and nitrites is also a mechanism to store biological NO [12], but other sources as the foods have to be considered since nitrates and nitrites are present naturally in some foods and they seem to contribute to NO physiological effects [13–15].

2.1. Chemical structure

NO is composed of oxygen and nitrogen with a double covalent bond. The nitrogen atom lacks of one electron in the sp2 orbital (Fig. 1), turning NO a high reactive molecule, however it can stay as nitrosonium anion (NO^+) [16]. NO is electrically neutral, which allows NO to cross biological membranes with a diffusion rate of 848 square micrometers per second in the aortic wall [17]. This property favors greatly its function as second messenger. Nevertheless its action ratio is confined by its high reactivity, which shorts dramatically NO half-life to 1–10 s [18]. Therefore, its production and half-life will depend on the type of tissue (i.e. capacitance versus resistance arteries) and the pathophysiological state of the tissue.

2.2. The nitric oxide synthases

NO is mostly produced by the NOS enzyme family: endothelial (eNOS), inducible (iNOS), neuronal (nNOS) and mitochondrial (mtNOS), being the former the isoform α of nNOS expressed in the inner mitochondrial membrane [19]. All the NOS are heterogeneous proteins coded by different genes in different chromosomes modified also by alternative splicing [20].

NOS are proteins that need to bind four cofactors for their proper function. These are the flavin adenine mononucleotide (FMN), the flavin adenine dinucleotide (FAD), the heme (iron protoporphyrin IX) and the tetrahydrobiopterin (BH4) [21,22]. The former is a pteridine with redox activity that works as an electron donor in the NO synthesis [23,24] having a raising interest due to its action on NOS and other physiological and pathological functions [25–29].

NOS have two domains with different activities. The N-terminus domain works as an oxygenase binding BH4, iron protoporphyrin IX and L-Arg. The C-terminus domain works as a reductase binding FMN, FAD, NADPH and calcium/calmodulin (Ca^{2+}/CaM). Ca^{2+}/CaM is needed to open the gate that allows the electron flux into the active center of the NOS [30–32].

2.2.1. The endothelial nitric oxide synthase

The eNOS or NOS III is activated by Ca^{2+} [33] since it has the Ca^{2+}/CaM-binding domain, a domain shared with nNOS [34,35]. It is expressed in endothelial cells to regulate blood flow [7,36]. The activation of eNOS is dual since needs the binding of Ca^{+2}/CaM but also the phosphorylation by phosphatidylinositol 3-kinase (PI3K/Akt) [37].

The eNOS is also expressed in fibroblasts [38], skeletal muscle [39], bone [40], motorneurons [41] and astroglia [42] where NO works as a neurotransmitter or a signaling molecule with different intracellular effects.

2.2.2. The inducible nitric oxide synthase

iNOS or NOS II is independent of Ca^{+2}/CaM since it lacks of the binding domain to CaM, therefore the regulation of iNOS is at the transcriptional level. iNOS is expressed in immune and glial cells when they are challenged [7,43], but it is also expressed in other tissues undergoing proinflammatory states [44–47]. iNOS participates in the immune response mainly contributing to induce apoptosis in transformed cells and pathogens. In brain iNOS is expressed by astrocytes, microglia and vascular cells releasing NO during hours or days [7,48,49].

2.2.3. The neuronal nitric oxide synthase

The nNOS was isolated initially from rat cerebellum [21,50] showing a wide distribution in brain [51,52]. It plays key roles in neuronal differentiation [53], pain [54], neuroendocrine function of the hypothalamus-hypophysis axis [55], sleep [56] and hippocampal function [57].

The nNOS has four different isoforms. The nNOSα and nNOSμ are anchored to intracellular structures of the neurons by a PDZ domain. The nNOSγ and nNOSβ are cytoplasmatic. Regarding synaptic plasticity, the PDZ domain is critical since it allows nNOS anchoring in the postsynaptic ending. It is due to the binding of the nNOSα to the postsynaptic density protein 95 (PSD-95), which allows its interaction with NMDA [58–61].

2.3. Physiological functions of nitric oxide

NO binds to the heme group of proteins, such as guanylyl cyclase (GC). The most of the known effects of NO are due to activation of GC and the production of guanosine 3′,5′-cyclic monophosphate (cGMP), but there are other effects independent of GC activation that play key roles in systemic and brain physiology.

2.3.1. Vascular tone control

The soma of the neurons has a mean distance of 15 μm to the closest vessels to maintain the proper oxygen and nutrient supply [62]. Therefore, neurons are absolutely dependent on the brain vascular tone. The blood pressure induces shear stress on the apical part of endothelial cells activating mechanosensitive channels that allows an influx of Ca^{2+} that activates eNOS (Fig. 2). NO released in the intima diffuses to the tunica media relaxing vascular smooth muscle cells (VSMC). In VSMC NO activates GC that produces cGMP [63]. cGMP binds to cGMP-dependent protein kinase I (PKG I), which phosphorylates the alpha subunit of the Maxi-K^+ channel allowing the output of potassium (K^+) that hyperpolarizes and relaxes VSMC [64] (Fig. 2). The NO vasorelaxant effect is increased by activating the Ca^{+2}-ATPases from the reticulum [65] and the phosphatase that dephosphorylates to the myosin light chain kinase [66].

2.3.2. Hemostasis control

When there is a hemorrhage the blood passes from liquid to solid state forming a clot that will prevent its extravasation. The different mechanisms that converge to avoid hemorrhages are termed hemostasis that also includes the subsequent clot degradation by plasmin. Under normal conditions, blood coagulation is inhibited physiologically by the endothelium of the vessels among other mechanisms by NO, which impairs the ADP-induced platelet aggregation by a cGMP-dependent effect [67] (Fig. 3). Therefore the impairment in NO production will not

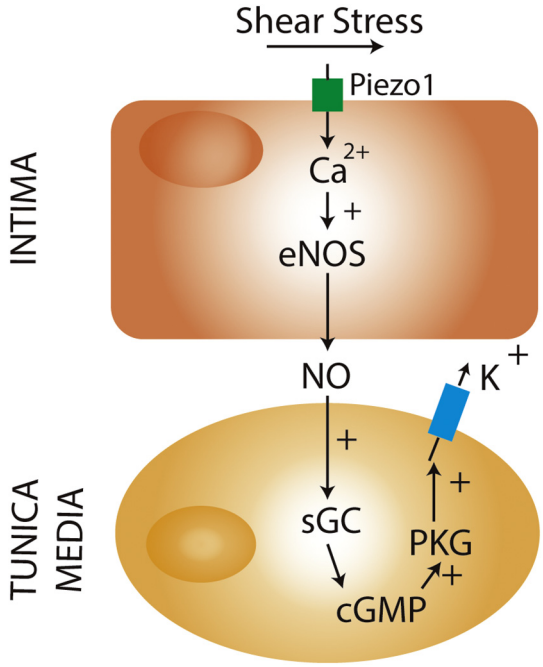

Fig. 2. NO is a vasorelaxant agent. Blood flow induces shear stress on the intima opening Piezo1 channels. It produces the entrance of Ca^{2+} inside endothelial cells activating eNOS. NO diffuses to the tunica media, where it activates the production of cGMP. Therefore PKG I phosphorylates the Maxi-K^+ channel hyperpolarizing and relaxing VSMC.

just affect to the vascular tone but also can favor a prothrombotic state.

2.3.3. Immune functions

NO has a Janus behavior regarding the immune system. The eNOS produces NO to induce vasodilatation and therefore leukocyte influx allowing the vigilance by the immune system, but it impairs leukocyte diapedesis [68] working as an immune brake under physiological conditions. However in both innate and acquired immunity the activation of the leukocytes yields to the expression of iNOS to induce directly damages in the pathogens or abnormal cells but also activating the immune response. Even NO can yield to the onset of a sheptic shock by the general vasodilatation and cytokine production [69].

In particular NO is an anti-inflammatory molecule under resting conditions [70,71] but once that leukocytes express iNOS the NO contributes to the effects and maintenance of the inflammatory response by regulating cytokine release [72] The regulation of inflammation by NO is highly relevant to brain since microglia and astrocytes can express iNOS [73]. Microglia, the monocyte-macrophage brain system, carried out a protective role needed to maintain a healthy brain, in fact microglia go through the whole brain each 24 h cleaning the metabolic rests from the brain parenchyma. But sporadic traumatic brain injuries or boxing, which are associated to brain inflammatory responses, increase dramatically the risk of neurodegenerative processes [74–76] and when the onset of neurodegenerative diseases is produced its role has a high pathological contribution to these diseases, as it will be discussed later in this review.

The direct noxious effects of NO on pathogens, transformed cells or even healthy cells are due to the generation of reactive nitrogen species (RNS), which react with multiple targets causing DNA damages [77], activation or inactivation of different transcription factors [78,79], the impairment of physiological metabolism [80,81] and apoptosis [7,82–84].

2.3.4. Nitric oxide as neurotransmitter

NO can be released by both pre- and postsynaptic endings. In the most parts of the brain NO is produced postsinaptically and mainly associated to NMDAR activation working as retrograde neurotransmitter. However, NO is also released by the presynaptic ending in peripheral nitrergic nerves acting as anterograde neurotransmitter or neuromodulator.

2.3.4.1. Nitric oxide as anterograde neurotransmitter. In nitrergic nerves the action potentials arrive to the presynaptic ending and open the voltage-gated Ca^{+2} channels (VGCCs) and therefore Ca^{+2} activates nNOS, playing a key role in different neuronal activities mainly in the control of the gastrointestinal motility by the enteric nervous system [85] and in pain transmission in spinal cord, where nitrergic interneurons located in laminae II and III of the Substantia Gelatinosa of Rolando regulate the transmission between the nociceptive primary and secondary neurons along the spinothalamic lateral pathway [86].

2.3.4.2. Nitric oxide as retrograde neurotransmitter. Glutamate activates NMDAR in hippocampal glutamatergic synapses (Fig. 4). This receptor

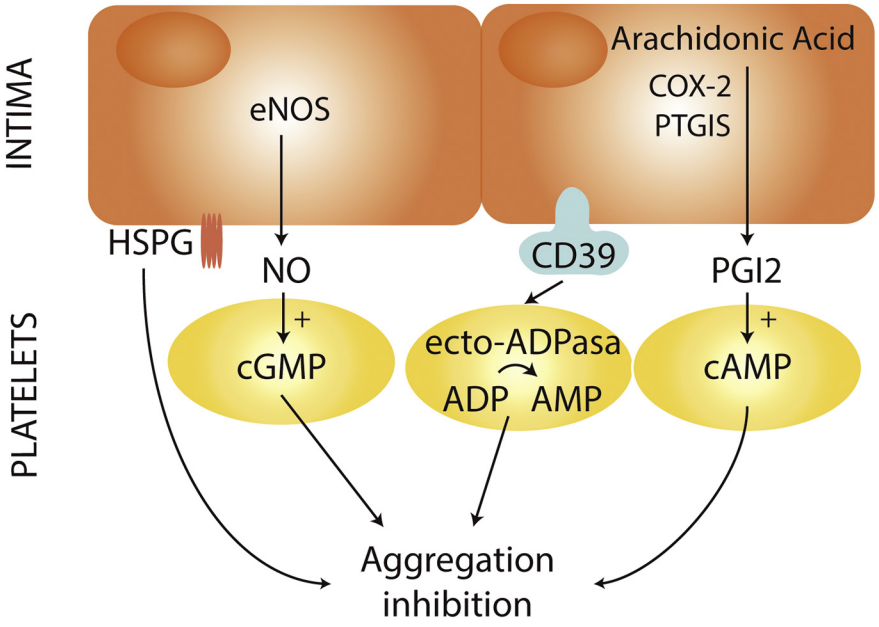

Fig. 3. NO inhibits platelet aggregation. Blood coagulation is inhibited physiologically by the endothelium of the vessels throughout the production of NO, prostacyclin PGI2 and ecto-ADPase (or ectonucleotidase CD39) increasing cGMP and cAMP platelet levels. Likewise, the endothelium expresses in its apical surface constitutively a coagulation inhibitor similar to heparin termed heparan sulfate, a component of proteoglycans (HSPG).

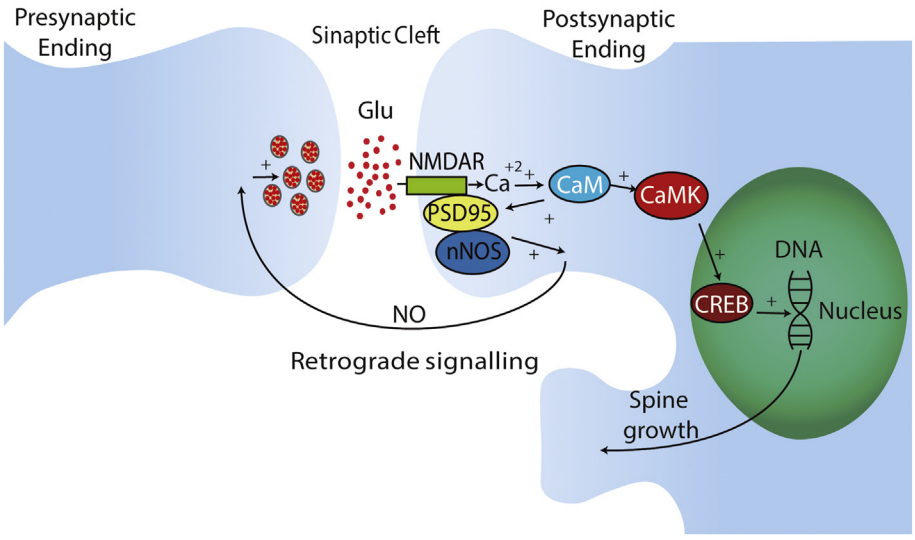

Fig. 4. NO effect on LTP. Glutamate activates NMDAR allowing the Ca^{+2} entrance. It will produce the release of NO that works as retrograde neurotransmitter maintaining glutamate exocytosis from the presynaptic ending, yielding to LTP. LTP induces spine growth by the resulting CREB activation.

needs two different stimuli for its activation: sodium (Na^+) entry to depolarize the postsynaptic membrane and glutamate and glycine binding. Then the magnesium ion is released from the top of the channel allowing the influx of cations, mainly Na^+ and Ca^{2+}. Na^+ depolarizes the postsynaptic membrane and Ca^{+2} binds to CaM and activates nNOS, producing NO. As a gas NO can diffuse from the postsynaptic ending to the presynaptic where stimulates the release of vesicles by a GC-independent mechanism [87,88]. It will form an activation loop termed long term potentiation (LTP) [89,90], which is the physiological mechanism of learning and memory (Fig. 4). This mechanism of glutamatergic activation and NO release acting as retrograde neurotransmitter in the presynaptic has been also reported in another brain centers such as the basal ganglia where controls the ACh release.

2.3.5. Nitric oxide in memory and learning

The open of NMDAR and the consequent Ca^{+2} input also produces the activation of the Ca^{+2}/CaM-dependent protein kinases (CaM kinases) II and IV in the postsynaptic ending (Fig. 4). CaM kinase II phosphorylates the glutamatergic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, which considerably increases the entry of Ca^{+2}. CaM kinase IV phosphorylates the transcription factor cAMP-response element binding-protein (CREB) [91], activating the expression of genes related with learning and memory (Fig. 4). The maintenance of this signaling is extended over time by the release of NO from the postsynaptic ending and by the autophosphorylating capacity of the CaM kinases.

It is important to remark that not always NO is producing LTP or CREB activation. Hippocampus stores memory by CREB activation and spine growth stimulation but they will be targeted depending on the potency of the loop of presynaptic spikes-glutamate-NO. This loop can produce three types of responses depending on the frequency of the incoming pulse trains: i) presynaptic spike pulses with frequencies from 1 to 10 Hz lead to long-term depression (LTD) at the postsynaptic ending avoiding memory formation; ii) presynaptic spike pulses with frequencies from 50 to 100 Hz lead to LTP, whose activity is largely maintained but only at the postsynaptic ending; iii) presynaptic spike pulses with frequencies higher than 100 Hz and up to 200 Hz lead to LTP, whose activity is maintained for days at both the presynaptic and postsynaptic endings [92–94].

2.3.6. Nitric oxide induces dendritic spine growth

NO binds to the heme group of the heme-regulated eukaryotic initiation factor 2α (eIF2α) kinase (HRI) producing its activation [95]. HRI is one of the four kinases that phosphorylates eIF2α and is located in the dendritic spines [96–98]. Its phosphorylation arrests the translation of the most of the mRNAs undergoing different stress situations. The exception is those mRNAs containing more than one upstream AUG (uAUG) in the 5′ untranslated region (5'UTR) because p-eIF2α activates their translation. This mechanism focused the energy and signaling pathways in the expression of those proteins needed in such stress conditions. LTP induces a physiological stress in the postsynaptic ending to activate the spine growth and the mechanism used is the activation of HRI by NO [99–101] (Fig. 5). Therefore the activation of NMDAR as showed in Fig. 4 also has a local effect in the postsynaptic ending. Here NO induces eIF2α phosphorylation to promote the translation of the poly-AUG mRNAs that are stored in the granules of stress and processing bodies located at the base of the spines. HRI is the only eIF2α kinase regulated allosterically by NO but the other three

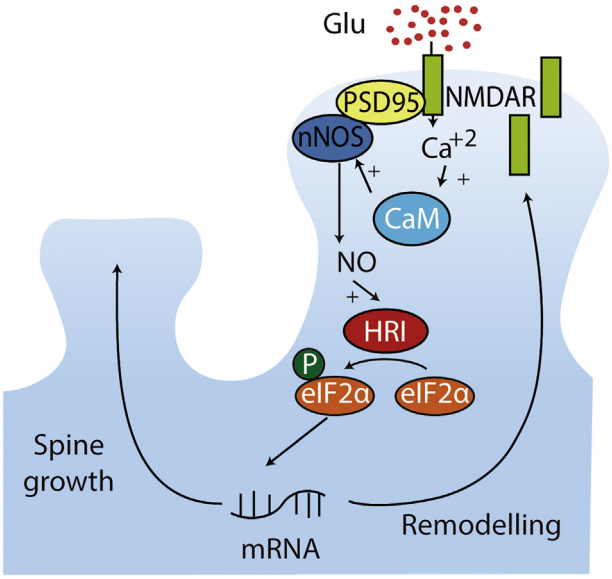

Fig. 5. NO effect on spine protein translation. Glutamatergic signaling triggers NO release. NO activates the enzyme HRI that phosphorylates the eIF2-alpha. P-eIF2-alpha induces the translation of these mRNAs bearing several AUG in their 5'-UTR, which are proteins needed for the proper function of the spines and allowing their growth.

Table 1
Nitrosylation of signaling pathway proteins.

Molecule	Physiological function	Nitrosylation effect	Ref.
Glyceraldehyde-3-phosphate dehydrogenase (GAPDH)	Glycolysis and transcription, DNA replication, RNA transport and apoptosis	Loss of the protective function towards mRNAs, which in the case of L13a causes loss of activity of GAIT complex leading to apoptosis	[105]
S100-A8	Regulation of immune response and inflammatory processes	GAPDH nitrosylation	[106]
S100-A9	Regulation of immune response and inflammatory processes	GAPDH nitrosylation	[106]
DNA lyase	DNA repair and regulation of transcriptional factors	Transport from nucleus to cytoplasm	[137]
Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)	Transcription factor involved in immunity, differentiation, cell growth, apoptosis, tumorigenesis and inflammation	Inhibition of DNA binding	[109]
Glypican-1 (GPC1)	Cell surface proteoglycan that participates in signaling pathways	Facilitation of the autocleavage of glypican-1 heparan sulphate, inducing neurodegeneration	[138]
Hypoxia inducible factor 1α (HIF1α)	Transcriptional regulator of cellular response to hypoxia	Increased transcriptional activity through a gain of stability	[110]
Cyclin-dependent kinase 2 (Cdk2)	Cell cycle, being crucial in meiosis	Inhibition at high doses and activation at low doses	[107]
Histone deacetylase 2 (HDAC2)	Deacetylation of lysine residues in histones	Loss of dimerization causing an increase of expression	[139]
Catenin β-1	Wnt signaling pathway and cell adhesion	Adherent junctions disassembly	[140]
Insulin-degrading enzyme (IDE)	Intracellular peptide signaling	Enzymatic inhibition	[141]
p53	Regulation of cell-fate through several pathways	Enzymatic inhibition at high doses and activity stimulation at low doses	[142]
Phosphatase with sequence homology to tensin (PTEN)	Inhibitor of Akt pathway	Enzymatic inhibition increasing akt activity	[143]
Protein kinase B (Akt)	Regulatory enzyme through serine/threonine phosphorylation	Enzymatic inhibition favoring apoptosis	[144]
Cyclin dependent kinase 5 (Cdk5)	Cell cycle regulation	Increased apoptosis	[108]
Dexamethasone-induced Ras-related protein 1 (RASD1)	Small GTPase of Ras	Increased enzymatic function	[145]
Egl nine homolog 1 (EGLN1)	Synthesis of hypoxia-inducible factor	Inhibition of enzymatic activity	[146]

eIF2α kinases can be also activated indirectly by NO [102], and may be they are playing similar roles in spine growth.

2.3.7. Nitric oxide promotes presynaptic growth

NO has a trophic effect in the presynaptic ending as it has been demonstrated when NMDAR is activated inducing the growth of presynaptic filopodia [103]. In addition, NO regulates presynaptic plasticity in gabaergic and glutamatergic neurons [104].

2.3.8. Nitrosylation

S-nitrosation or S-nitrosylation consists of the NO binding to amino acids preferently to the thiol of the cysteines forming S-nitroso amino acids. Nitrosylation is a post-translational mechanism to regulate the function of the proteins, mainly enzymes whose catalytic activity is decreased but also affects to other proteins.

Nitrosylation affects to proteins and transcription factors involved in different signaling pathways (Table 1). Some of these proteins are regulating nucleus activity such as GADPH [105,106] and its nitrosylation yields to apoptosis, a common fate after the nitrosylation of cyclins that classically control cell cycle [107,108]. In other cases the nitrosylation impairs the binding of some transcription factors such as NF-κB [109] which impairs p38 MAPK signaling and the onset of the inflammatory response. In other cases when stressful situations, such as hypoxia, can compromise cell viability nitrosylation increase the activity of HIF1α [110].

The nitrosylation of metabolic protective proteins (Table 2) is a mechanism to regulate the redox state of the cells [111], the proteosoma activity [112–114], the reticular stress and the unfolded protein response [115–118] or even to decrease the NO production by eNOS [115,117].

It is in the regulation of the intracellular signaling related with cell death where nitrosylation has a broad number of targets (Table 3) directed to caspases [114,119–121], adhesion molecultes such as MMP-9 [122], death receptors activation [123,124], transcription factors associated to stress activated kinases [125] or even to increase the protective role of Bcl-2 [126,127].

The nitrosylation of metabolic enzymes (Table 4) decreases polyamine synthesis [128], which are regulators of cell metabolism. It also increases the metabolism of arachidonic acid throughout prostaglandin G [129], favors the fatty acids β-oxidation [130] and regulates structural proteins [106,131,132]. Interestingly it produces a maintained Ca^{2+} leak in some Ca^{2+} channels such as ryanodine receptor and KCJN2 [133,134] that would be helping to maintain a contractile tone or even to favor neurotransmitter release. On the contrary, other cationic channels are inhibited with a regulating function of the glutamate signal [135].

Nitrosylation will affect in different degree and with different consequences to the physiological functions of NO, resulting in the modulation of the vascular tone, the platelet aggregation, the immune response, the spine growth and the memory consolidation. Moreover S-nitrosylation is able to determine the fate of the cells throughout its effect on the proteins that control apoptosis. Interestingly S-nitrosylation would be also a mechanism to store NO since S-nitrosylation of plasmatic albumin is considered a reversible process [136].

3. Oxidative stress

A free radical is a molecule with one or more unpaired electrons in their last orbitals making it an unstable molecule that looks for electrons from nearby molecules. They are usually by-products of oxygen metabolism being termed reactive oxygen species (ROS). ROS are produced in both physiological and pathological conditions.

ROS physiological production at very low concentrations regulates mitochondrial activity, transcription factors, signaling pathways, LTP regulation and even vascular tone by NADPH oxidase (NOX) [153–156]. Also in the physiological immune response ROS are released at high concentrations during the respiratory burst by the NOX from leukocytes and microglia [157,158].

The pathological production of free radicals is high and continuous generating oxidative stress. Oxidative stress is the consequence of the imbalance between ROS production and their elimination by the antioxidant defenses. ROS react with proteins, lipids and nucleic acids

Table 2
Nitrosylation of metabolic protective proteins.

Molecule	Physiological function	Nitrosylation effect	Ref.
Thioredoxin	Redox reactions	Depending on the nitrosylated residue: induction of a transnitrosylase activity or denitrosylase activity	[111]
Parkin	E3 ubiquitin ligase enzyme for ubiquitination	Loss of function	[112]
Heat shock protein 90-α (Hsp 90α)	Chaperone with a function in regulation, homeostasis and maturation of specific proteins	Loss of its ATPase activity and eNOS activation	[117]
Ubiquitin-like protein ISG15 (ISG15)	Ubiquitin protein with innate immune response function	Increased activity	[113]
Tyrosine-protein phosphatase non-receptor type 1 (PTPN1)	Unfolded protein response in endoplasmic reticulum	Loss of activity	[118]
Haemoglobin subunit β	Oxygen transport	Oxygen transport	[147]
X-linked inhibitor of apoptosis protein (XIAP)	Caspase inhibitor and E3 ubiquitin-protein ligase inhibitor that modulates multiple cellular functions	Downregulation E3 ubiquitin-protein ligase activity	[114]
Heat shock protein 90-β (Hsp90β)	Chaperone with functions in regulation, homeostasis and maturation of specific proteins	Loss of its ATPase activity and eNOS activation	[115]
N-ethylmaleimide sensitive factor (NSF)	ATPase working in vesicular transport, related to AMPAR as a stabilizer and recycler protein in the postsynaptic membranes	Increased binding to the AMPAR GluR2 subunit, protecting from apoptosis	[148]
Protein-disulphide isomerase (PDI)	Transport and maturation of unfolded proteins	Inhibition of its enzymatic activity	[116]
Annexins	Anticoagulant protein	Unknown	[106]

damaging cells and yielding to apoptosis being tightly associated to the onset and progression of neurodegenerative processes [159,160] and also playing a key role in ischemic brain stroke [7,161].

The relevance of oxidative stress in neurological diseases is tightly related with peroxynitrite production and nitrative damages as explained in the corresponding subsequent sections. But the specific contribution of free radicals and the antioxidant defenses againgst oxidative stress in neurological diseases is reviewed in this section.

3.1. Reactive oxygen species

The ROS in systemic and brain tissues are $O_2\cdot^-$, hydroxyl radical (OH·), alkoxyl radical (RO·), peroxyl radical (ROO·), hydro-peroxyl radical (HO·) and those able to generate free radicals such as hydrogen peroxide (H_2O_2), aldehydes (HCOR), hydrochlorous acid (HOCL), organic peroxides (ROOH), singlet oxygen ($^1O_2$), ozone (O_3) and NO [159].

The main ROS are $O_2\cdot^-$, OH· and H_2O_2. $O_2\cdot^-$ is highly reactive oxidizing the most of cell molecules [162] but its ability to cross biological membranes is highly limited due to its negative charge. H_2O_2 can cross biological membranes with relative ease. It is not a free radical sensu stricto but generates OH· by a Fenton reaction [163,164].

3.1.1. Reactive oxygen species production

ROS are produced by different mechanisms being the mitochondria, through the electron transport chain, the higher physiological source of $O_2\cdot^-$ and H_2O_2 [162]. The efficiency of electron transport chain is reduced with age, which means an increased production of $O_2\cdot^-$ and H_2O_2 [165]. The pathophysiological consequences are lipid peroxidation in the brains from patients of Alzheimer's disease (AD) [166], Parkinson's disease (PD) [167], and Lewy body disease (LBD) [168], in the cerebrospinal fluid (CSF) from patients of Huntington's disease (HD) [169], and multiple sclerosis (MS) [170], and in the plasma from patients of amyotrophic lateral sclerosis (ALS) [171]. These findings mirror a dramatic damage to the functionality of the membranes in these diseases. Moreover oxidative damage of proteins, RNA and DNA are present in the brains of AD patients [172,173] and other neurodegenerative diseases [174–176].

Other relevant ROS sources are NOX [177–180], peroxisomes [181,182], the neuronal oxidases such as monoaminoxidases (MAO) [183] and xanthine oxidase [184], and the proinflammatory lipo- and cyclo-oxygenase [185]. All of these alternative sources of ROS are also involved in neurodegenerative processes associated to aging. Thus the NOX from microglia and astrocytes has been reported to contribute to neuronal death in AD [186,187]. Similar results have been obtained in dopaminergic neurons contributing to the onset of PD [188], in microglial activation in stroke to define the fate of the ischemic penumbra area [189] or in the involvement of microglial cells in the progression of ALS [190].

Table 3
Nitrosylation of proteins involved in apoptosis and autophagy.

Molecule	Physiological function	Nitrosylation effect	Ref.
X-linked inhibitor of apoptosis protein (XIAP)	Caspase inhibitor and E3 ubiquitin-protein ligase inhibitor that modulates multiple cellular functions	Downregulation of E3 ubiquitin-protein ligase activity	[114]
Caspase-3	Apoptosis signaling pathway	Protection against apoptosis induced by Fas	[119]
Caspase-8	Apoptosis signaling pathway	Protection against apoptosis induced by Fas	[120]
Caspase-9	Apoptosis signaling pathway	Protection against apoptosis induced by Fas	[121]
Matrix metalloproteinases 9 (MMP-9)	Endopeptidases that degrades extracellular matrix proteins	Enzymatic activation leading to apoptosis	[122]
B-cell lymphoma 2 (Bcl-2)	Inhibitor of apoptosis and inducer of autophagy	Increase of its antiapoptotic activity and decrease of its pro-autophagic activity, due to an increased affinity with Beclin-1	[126,127]
c-Jun N-terminal kinases (JNK1)	Kinase inducer of autophagy	Decreased activity	[125]
Inhibitor of nuclear factor kappa-B kinase subunit beta (IKKβ)	Kinase inducer of autophagy	Decreased activity	[125]
FLICE inhibitory protein (FLIP)	Protein with an antiapoptotic function through competitive binding with Caspase-8 for FADD	Resistance to ubiquitination, therefore increase in its antiapoptotic function	[149]
Dynamin-related protein 1 (Drp-1)	Inducer of mitochondrial fission	Increased activity leading to apoptosis	[150]
Fas	Transmembrane protein, apoptosis inducer	Increased activity leading to apoptosis	[123]
Apo2L/TRAIL death receptor DR4 (DR4)	Receptor of the extrinsic apoptotic pathway	Increased activity leading to apoptosis	[124]

Table 4
Nitrosylation of metabolic proteins, ion channels and structural proteins.

Molecule	Physiological function	Nitrosylation effect	Ref.
Ornithine decarboxylase (ODC)	First enzyme of polyamine biosynthesis	Loss of function	[128]
Prostaglandin G/H synthase 2 (PTGS2)	Enzyme which takes part in prostanoid synthesis	Enzymatic activation	[129]
Very long-chain specific acyl-CoA dehydrogenase, mitochondrial (VLCAD)	Fatty acid catalytic enzyme	Improved its catalytic efficiency	[130]
S-adenosylmethionine synthase isoform type-1 (MAT1A)	Takes part in S-adenosylmethionine formation	Enzymatic inactivation	[151]
Moesin	Takes part in the plasma membranes' cytoskeletal structure	Unknown	[106]
Ezrin	Protein of connection between cytoskeletal structures of the plasma membrane	Unknown	[106]
Vimentin	Type of intermediate filament with a role in anchoring the organelles in the cytosol	Unknown	[106]
Tripartite motif-containing protein 72 (TRIM72)	Cell membrane repair protein specific in muscle	Protection against oxidative degradation	[131]
α-1-syntrophin (SNTA1)	Adapter protein, may organize the localization of some membrane proteins	Negative regulation	[132]
Ryanodine receptor 1 (RyR1)	Sarcoplasmic Ca2+ channel	Conformational changes, leading to leaky channels	[133]
Inward rectifier potassium channel 2 (KCNJ2)	Membrane channel, takes part in excitability and the formation of action potential waveform in muscle and neuronal cells	Structural modification that leads to leaky channels	[134]
Pannexin	GAP channel and hemichannel component, regulating Ca2+ homeostasis	Inhibition of the channel currents and ATP release	[152]
NMDA receptor NR1 subunit	Modulator of the NMDA channel	Inhibits receptor activation, which causes the channel to be closed	[135]
NMDA receptor NR2A subunit	Modulator of the NMDA channel	Inhibits receptor activation, which causes the channel to be closed	[135]

3.1.2. Antioxidant defenses

Neurons are postmitotic cells able to live over 80 to 100 years, which means a long exposure to oxidative stress. Therefore neurons metabolize glucose by the pentose phosphate pathway [191] in order to increase the neuronal reducing load, i.e. NADPH that is fundamental for the protein-based antioxidant systems and glutathione turnover. On the other hand the antioxidant defenses in brain are the same than in systemic tissues. They are constituted by detoxifying enzymes and molecules that work as free radical scavengers. The most important constitutive antioxidant defenses are formed by superoxide dismutase (SOD), catalase, reduced glutathione (GSH) and thioredoxins. These enzymes are expressed in all the brain cells in order to protect neurons against ROS.

3.1.2.1. Superoxide dismutase. SOD are enzymes that catalyzes the conversion of $O_2\cdot^-$ into H_2O_2. SOD are classified into three groups according to the metallic cofactor needed by each SOD. Copper (Cu) and Zinc (Zn) binding SODs are located at the cytoplasm (SOD1) or extracellularly (SOD3), and Iron (Fe) or Manganese (Mn) binding SOD is located at the mitochondria (SOD2) [192–194].

Apart from its pathological role in some genetics forms of ALS [195] in other neurodegenerative diseases its expression is enhanced as in AD [196,197] or PD [198] in order to eliminate the $O_2\cdot^-$ burst.

3.1.2.2. Glutathione. GSH is a tripeptide consisting of glutamate, cysteine and glycine with a high antioxidant ability [199]. When oxidized (GSSG) it is reduced to 2 GSH by glutathione reductase regenerating its antioxidant activity. GSH is one of the main antioxidant enzymes in the brain [200–202], but it is more abundant in astrocytes [203,204]. Consistently GSH is depleted in AD [205] and the induction of GSH depletion or the upstream redactor source NADPH correlate with neuronal damages in AD transgenic mouse models [206,207].

3.1.2.3. Catalase. Catalase converts H_2O_2 into H_2O and O_2 being one of the most active enzymes of the cell. It is located at the peroxisomes, the major organelles for H_2O_2 detoxification [134,139]. Catalase also detoxifies the cell from phenols and alcohols [208,209]. Its activity is decreased in the brain and plasma of AD patients [210,211]. Interestingly catalase can be inactivated by the intracellular binding of amyloid β-peptide (Aβ) aggregates triggering the Aβ neurotoxicity due to oxidative stress [212]. Catalase activity is also reduced in the basal nuclei of PD patients [213], and in plasma from ALS patients [214] suggesting an etiologic contribution of H_2O_2 in these neurodegenerative diseases.

3.1.2.4. Thioredoxins. Thioredoxin (Trx) system is composed of Trx, Trx reductase (TrxR) and Trx components are nicotinamide adenine dinucleotide phosphate (NADPH). TrxR catalyzes disulfide reduction in Trx with NADPH as cofactor. Trx are a group of proteins able to reduce oxidized molecules. Their protective activity is based in the thiol groups of their cysteines [159]. Reduced Trx are regenerated by Trx reductases [215,216]. Moreover it works as a signaling molecule [217]. Trx is depleted in AD brains [216,218] and PD mouse models [219,220].

4. Peroxynitrite

NO is modified in the cells and tissues forming nitrites (NO_2^-) and nitrates (NO_3^-). NO pathological effects are due to its secondary intermediates mainly peroxynitrite anion (ONOO-) a kind of RNS. NO reacts with $O_2\cdot^-$ forming ONOO- that is not impaired by SOD since $O_2\cdot^-$ affinity is ten times higher for NO than for SOD [221,222]. Therefore ONOO- formation avoids the action of the antioxidant systems. ONOO– has an action radius of 100 dm but it is very reactive resulting in a quite short half-life of 1–20 ms [221]. It can be scavenged by reacting with CO_2/bicarbonate to yield nitrosoperoxycarbonate ($ONOOCO_2^-$) [223]. It is thermodynamically unstable however some authors consider that CO_2 would be contributing significantly to eliminate ONOO- [223].

4.1. Nitration

Nitration consists of the addition of a nitro group (NO_2) [259]. The peroxynitrous acid (ONOOH) is the protonated form of ONOO- that nitrates biomolecules [260]. It is the source of nitrogen dioxide ($\cdot NO_2$) and $OH\cdot$ making ONOOH both a nitrating and an oxidant agent but the ability to cross membranes of ONOO- is significantly lower than that of $\cdot NO_2$.

ONOO- nitrates lipids, proteins and nucleic acids [159]. ONOO- reacts with proteins affecting irreversibly their physiological functions

Table 5
Nitration of signaling pathways proteins.

Molecule	Physiological function	Nitration effect	Ref.
Histone deacetylase (HDAC2)	Epigenetic modulator of transcription through histones modification	Reduction of activity	[224]
p53	Regulation of cell-fate through several pathways	Inhibition of enzymatic activity	[225]
Protein kinase C (PKC)	Regulatory enzymes through serine/threonine phosphorylation	Inhibition of enzymatic activity	[226]
c-Jun NH_2-terminal kinase (JNK)	Crucial enzyme in several pathways related to cell proliferation, apoptosis and differentiation	Activation	[227]
Presenilins	Enzyme with transcriptional activation function through cleavage	Increased enzymatic activity	[228]
Ribonucleotide reductase R2 subunit	Enzyme with a DNA synthesis and repair function	Enzyme inactivation	[229]
Protein kinase G-1α	Enzyme mediator of NO pathway	Decreased enzymatic activity	[230]
Peroxiredoxin 2	Peroxide detoxification and player in peroxide signaling	Resistance to oxidation and increase of its enzymatic activity	[231]
Peroxiredoxin 6	Peroxide detoxification and player in peroxide signaling	Reduction of activity	[232]
Eukaryotic translation elongation factor 2	Translation of protein	Reduced protein synthesis	[232]

Table 6
Nitration of protective and harmful proteins.

Molecule	Physiological function	Nitration effect	Ref.
Manganese superoxide dismutase (MnSOD)	Dismantle superoxide by-products	Inactivation	[233,234]
Heme oxygenase (HO)	Degradation of heme groups	Concentration dependent loss of activity	[235]
Prostacyclin synthase (PGI(2)-S)	Regulation of blood pressure through the synthesis of prostacyclin	Inhibition of activity	[236]
Fibrinogen	Regulation of blood pressure in case of tissue or vascular damage	Acceleration of clot formation	[237]
Glutathione S-transferase (GST)	Oxidative stress protection through generation of GSH	Increased enzymatic activity	[238]
Albumin	Major protein in human plasma and CSF with a transport and protective function	Loss of function	[239]
Aβ	Neurotoxicity in AD	Enhanced aggregation into cytotoxic oligomers	[240,241]
Prostaglandin endoperoxide synthase	Inflammation	Decreased enzymatic activity	[242]
Glutathione reductase	Exchange of GSSG to GSH	Decreased enzymatic activity	[243]
Hsp90	Chaperone regulating cell homeostasis and stress response	Apoptosis induction in motor neurons	[244]
Voltage dependent anion channel	Protein with a function in controlling calcium transport through the membrane	Concentration dependent loss of activity	[245]
Poly (ADP-ribose) synthetase (PARS)	Regulation of cell death	Activation	[246]
26 S Proteosome	Degradation of proteins	Decreased function	[232]
TCPB	Tubulin and actin chaperone	Loss of function	[232]
MTHSP75	Mitochondrial protein chaperone	Mitochondrial dysfunction	[232]

Table 7
Nitration of metabolic and structural proteins.

Molecule	Physiological function	Nitration effect	Ref.
Glutamine synthetase (GS)	Synthesis of glutamine from ammonia and glutamate, protecting from nitrogen reactivity	Loss of catalytic activity	[247]
Iron regulatory protein-1 (IRP-1)	Control of cellular iron homeostasis, modulating synthesis of proteins related with iron metabolism	Inhibition of aconitase activity and IRE-binding activity	[248]
Aldolase (ALDA)	One of the enzymes responsible of glycolysis	Impaired glycolytic activity	[249]
Cytochrome C (Cyt C)	Mitochondrial electron transport chain	Inhibition of peroxidase activity	[250]
Triose-phosphate isomerase (TPI)	Control of glycolysis by the isomerization of trioses	Loss of function	[232,251,252]
α-enolase	Glycolysis	Decrease of activity	[252]
Glutamate dehydrogenase	Urea cycle	Increased enzymatic activity	[253]
Cytochrome P450 2B1	NADPH-dependent electron transport pathway	Concentration dependent loss of activity	[254]
Tyrosine hydroxylase	Catecolamine synthesis	Decreased enzymatic activity	[255]
Actin	Cytoskeleton	Disorganization of actin filaments	[256]
Tau	Regulator of cellular structure through their interaction with microtubules	Increased aggregation	[257]
Surfactant protein A	Protein that stabilize the lung air-liquid interface	Decreased aggregation	[258]
Metavinculin	Cytoskeleton	Unknown	[232]

in signaling pathways (Table 5), cell protection (Table 6), metabolism and cell structure (Table 7). In some cases ONOO- has been found to stimulate endothelial cell proliferation and even to be neurogenic due to the activation of the Wnt signaling, but it is mostly associated with deleterious effects in neurological diseases and pathological processes such as AD or hyperalgesia. ONOO- at high concentrations induces cell death, which is related with the reactivity of the anion with different biomolecules [7,81].

Regarding proteins the amino acids that can be nitrated are tryptophanes and mostly tyrosines [247,259]. Tyrosine nitration or nitrotyrosination produces 3-nitrotyrosine after the binding of NO_2 to its phenolic ring (Fig. 6). It does not affect to all the tyrosines being estimated that only one to five of every ten thousand tyrosines are nitrated [261]. Nitrotyrosination is facilitated by the exposure of the tyrosines and the presence of negatively charged amino acids spatially close to tyrosines [262].

Nitrotyrosination is a post-translational modification mostly pathological that leads to the loss-of-function of the proteins or in particular cases to a gain-of-function [20]. It can also inhibit tyrosine phosphorylation [263], a mechanism used for many receptors to be activated. On the other hand nitrotyrosination would be also a mechanism to remove an excess of NO or even a labeling for those proteins

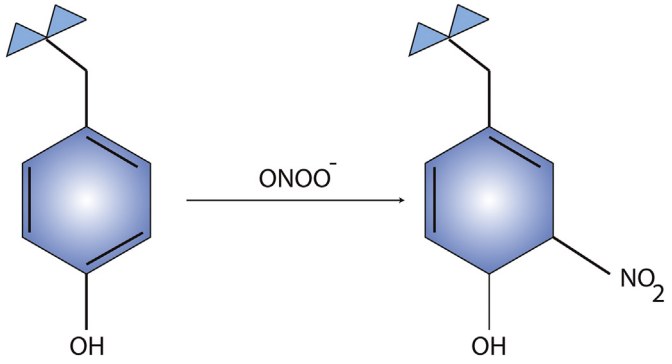

Fig. 6. Nitrotyrosination. The nitro group from ONOO- reacts with the phenol ring of the tyrosine residues rendering nitrotyrosine.

to be degraded by the proteosome [264]. In fact moderate nitrotyrosination has been observed in proteins from healthy people [161,228,239] reinforcing that nitration at low levels can accomplish the proposed physiological functions.

Leukocyte peroxidases are another biological source of ONOO- [265–267]. Peroxidases are activated when leukocytes are challenged as it happens with the production of $O_2\cdot^-$ and the iNOS expression during the respiratory burst [157,158] (Fig. 7). ONOO- participates in the immune response by nitrating proteins to induce damages on transformed cells and pathogens [268,269].

4.2. Nitration in neurological diseases

Brain is characterized by a high oxidative metabolism since it consumes an elevated rate of the O_2 of the body, being approximately 20% [270]. It has antioxidant defenses but also utilizes the most of antioxidants from the foods compared with other organs [271]. Moreover brain has a high amount of unsaturated lipids, such as the ganglioside GM1, which are targets for oxidation and peroxidation [272,273]. All this makes the brain susceptible to oxidative and nitrative damages that will be increased with aging. In fact ischemic brain stroke [7,161] and neurodegenerative diseases such as ALS [274], MS [275] and HD [276] are tightly associated to oxidative stress and protein nitrotyrosination. But among all of them AD and PD have the highest etiopathogenic relationship with nitrative stress [166,173,277–279], which together with the fact that AD and PD are the most prevalent neurodegenerative disease in aging its study is of great scientific and social interest.

4.3. Nitrotyrosination in Alzheimer's disease

AD is a progressive dementia caused by the extracellular

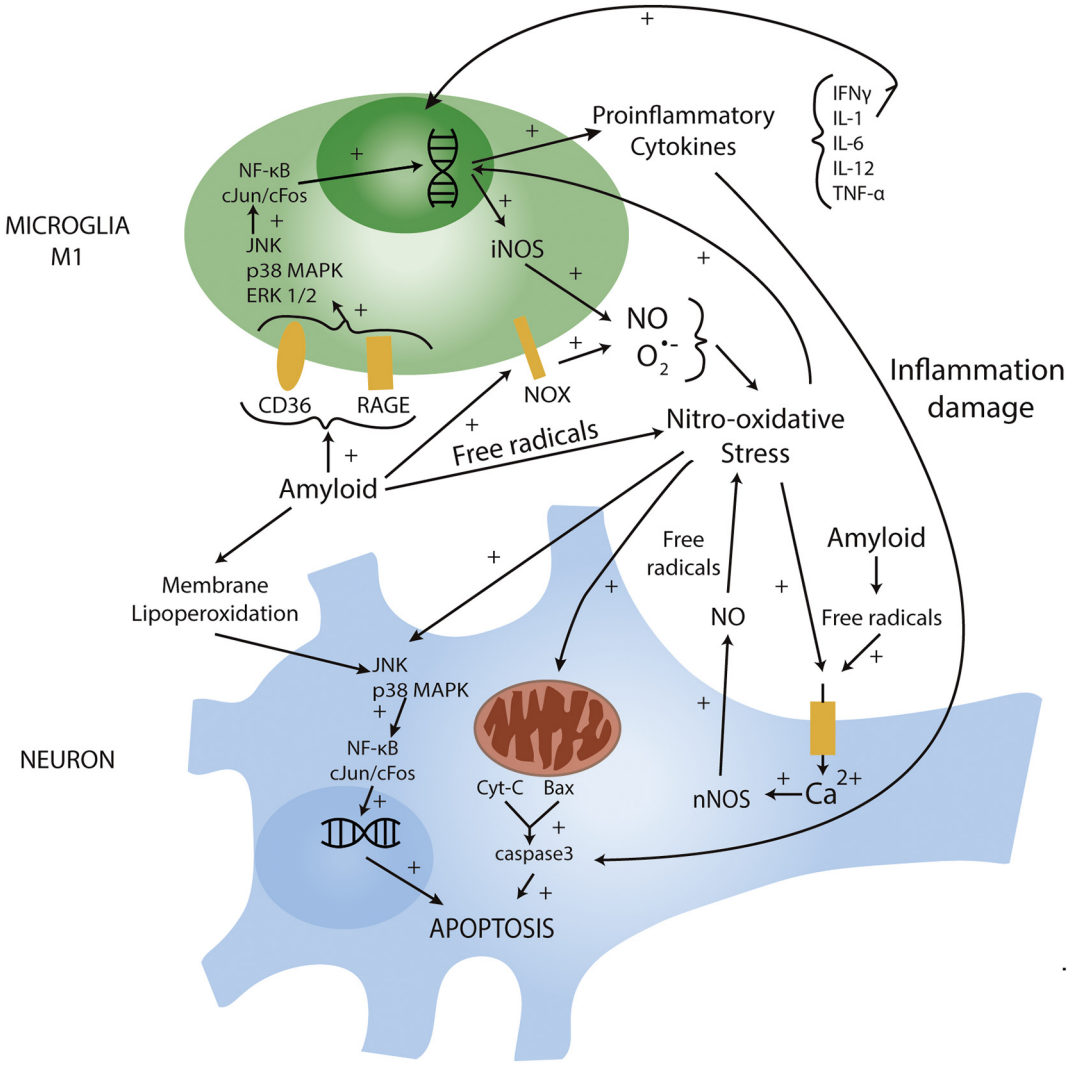

Fig. 7. Nitro-oxidative stress in brain. Aβ aggregates are recognized by the microglia throughout the CD36 and RAGE receptors. It activates microglia that produces NO by iNOS, superoxide by NOX and pro-inflammatory interleukins yielding to an insidious damage by nitro-oxidative stress on neurons.

aggregation into β-sheet of the Aβ, a product of the cleavage of the amyloid precursor protein (APP) [280]. The APP can be processed by the alpha-secretase activity, performed mainly by the enzyme ADAM10 [281], which cuts the APP by the amino acid 16 of the Aβ sequence preventing the release of Aβ and generating the non-amyloidogenic pathway of the APP cleavage. The pathophysiological processing pathway of APP that generates Aβ is initiated by the β-secretase activity, performed by the β-site APP cleaving enzyme type 1 (BACE1) [282], that cuts APP by the amino acid 1 of the Aβ sequence and the gamma-secretase activity, carried out by a protein complex where the catalytic activity resides in the presenilins (PS) [283], cutting mainly by the amino acids 40 and 42 of the Aβ sequence. Aβ misfolds forming oligomers, which are highly toxics [284], and fibrils [285] currently considered the less toxic forms of Aβ aggregates, which constitute the senile plaques [286].

Misfolded Aβ is able to produce H_2O_2 and OH· that will affect to neurons triggering the production of $O_2\cdot^-$, a process favored by transition metals [199]. Nitrotyrosination in AD brain was early reported [278] and currently a high number of nitrotyrosinated proteins have been reported in AD (Tables 5–7). The direct relationship between Aβ and nitrotyrosination was demonstrated by the intraventricular administration of Aβ in mice [287] and by the Aβ challenge to human neuronal and endothelial cells [81,232].

4.3.1. The role of nitric oxide synthases

The hippocampus, the center responsible for memory and learning, is one of the first centers to be affected in AD and it degenerates dramatically. APP, whose function is related to membrane adhesion and cell recognition, is highly expressed in neuronal synapses, allowing synaptic plasticity [288]. Since hippocampus is rich in APP expression the Aβ production is increased favoring its aggregation in an environment where glutamatergic signaling releases NO, making hippocampus especially susceptible to nitrative damage [278,289]. In fact increased nNOS expression correlates with neurons bearing neurofibrillary tangles, intracellular aggregates of tau protein characteristic of AD [251], in the entorhinal cortex and the hippocampus of AD patients [290]. In both cases the neuronal damage correlates with nitrergic neurons, as in an AD transgenic mouse model [291]. Moreover this stressful scenario will trigger the expression of the heat shock protein 90 (Hsp90), which is an activator of the nNOS, consequently increasing NO production [292,293]. These findings would be the results of a mechanism to compensate the lack of NO available for neurotransmission or the lack in the control of nNOS expression induced pathologically by Aβ [294].

Neurons that do not receive direct nitrergic transmission are also vulnerable to nitration since NO sources are widely spread in brain and NO can diffuse to almost all the brain neurons [295]. Therefore nitrotyrosination can be observed in almost the whole brain of AD patients in the most advanced stages of the disease and even in the CSF [296].

nNOS is not exclusive of neurons and it is also expressed in reactive astrocytes in the hippocampal formation from AD patients [297]. Moreover eNOS and iNOS are overexpressed in astrocytes from AD patients, findings also reported in APP23-AD transgenic mouse model [298–301]. In fact an association between AD and an eNOS polymorphism (Glu298Asp) has been reported [302–305].

The contribution of microglia seems to be even more relevant since these cells belongs to the monocyte/macrophage system and when they are reactive they start to produce $O_2\cdot^-$ due to the respiratory burst and express iNOS for long periods as found in the reactive microglia that surrounds the senile plaques. In fact the Aβ challenge on microglia induces NO production [306]. Moreover iNOS expression will be activated by the NF-κB and cJun/cFos intracellular signaling when proinflammatory or stressful conditions challenge microglia [307,308] (Fig. 7). It induces a loop of damage where citoquines are maintaining microglia in a reactive state that produces more NO and free radicals.

4.3.2. The loss of Ca^{2+} homeostasis and nNOS activation

There are studies demonstrating that mutations in genes unequivocally related to AD, such as presenilins, APP, apolipoprotein E and Ca^{2+} homeostasis modulator 1 (CALHM1) lead to alterations in Ca^{2+} homeostasis [309–317]. Even in skeletal muscle cells, Aβ induces an increase of intracellular Ca^{2+} through the inositol1,4,5-trisphosphate receptor (IP3R) [318]. Furthermore Aβ binds to NMDAR increasing Ca^{2+} entrance [241]. The result of these concurrent mechanisms is the increase in intracellular Ca^{2+} that yields to the pathological activation of nNOS, which will produce the nitrotyrosination of the proteins included in Tables 5–7 due to the pro-oxidant environment induced by Aβ.

4.3.3. The production of amyloid β-peptides

The main released Aβ species is composed of 40 amino acids ($Aβ_{1–40}$). But one tenth of the APP processing produces $Aβ_{1–42}$ [319–321]. It is a longer species with two extra amino acids at the C-terminus: alanine and isoleucine, which are hydrophobic and turn the $Aβ_{1–42}$ more prone to aggregate than $Aβ_{1–40}$ [322], being considered as the pathological starter of Aβ aggregation and AD onset [323–328]. Interestingly nitrotyrosination has been reported to play a key role in the shift of $Aβ_{1–42}/Aβ_{1–40}$ ratio during aging. It has been demonstrated that nitrotyrosination affects to gamma-secretase in AD patients and AD transgenic mouse model [228] and increases $Aβ_{1–42}$ production [228].

4.3.4. The aggregation of amyloid β-peptides

The misfolding of Aβ into β-sheet forming amyloid structures generates oligomers (mainly dimers to tetramers) and mature fibers. All of them are neurotoxic but the oligomeric forms have the greatest neurotoxicity [329]. Human Aβ has a tyrosine at the position 10 of its sequence susceptible to be nitrotyrosinated. In fact its nitrotyrosination has been demonstrated in vitro and in vivo [240,241]. Nitrotyrosinated $Aβ_{1–42}$ aggregates faster than the normal one. Moreover, nitrotyrosination stabilizes $Aβ_{1–42}$ oligomers, which are the most toxic forms of amyloid aggregates. Oligomers of nitrated $Aβ_{1–42}$ induce synaptotoxicity by binding to NMDAR, which induces a high Ca^{2+} entrance, impairs the physiological role of glutamate signaling and avoids spine growth [241].

4.3.5. Neuronal metabolism

Neuronal metabolism, i.e. glucose consumption, is dramatically compromised in AD [330–333]. γ-enolase/α-enolase, lactate deshydrogenase and triosephosphate isomerase (TPI) are proteins that works in glucose metabolism and have been also reported to be nitrotyrosinated in AD [232,251,252]. TPI regulates the glycolytic flow by the isomerization of the two trioses glyceraldehyde 3-phosphate (GAP) and dihydroxiacetone phosphate (DHAP) [334]. TPI nitrotyrosination reduces its isomerase activity therefore decreasing the glycolytic flow [251]. The reduction in its isomerase activity yields to methylglyoxal production, which is neurotoxic [80,251,335]. When TPI is nitrotyrosinated there is a change in its secondary structure folding into β-sheet and TPI aggregates [251]. Nitro-TPI aggregates interact with tau monomers to form the paired helical filaments (PHF) [251], which constitute the intracellular neurofibrillary tangles.

4.3.6. Neuronal transmission

One of the main pathological characteristic of AD is the cholinergic deficit [336]. Since TPI physiological function is decreased, the molecules in the downstream of the glucose metabolic pathway, such as acetyl-CoA, can be also affected. A depletion of acetyl-CoA, critical to produce ACh by the choline acetyltransferase, could result in ACh deficit [337]. Therefore, TPI nitrotyrosination could be playing a key role in the cholinergic deficit in AD.

On the other hand, synaptophysin has also been reported to be nitrotyrosinated in AD [287]. Synaptophysin is a component of the vesicles that release neurotransmitter, whichever damage in its function

will produce impairments in neurotransmission. Another finding that contributes to impair neurotransmission is the damage on the tubulin network by the nitrotyrosination of tau [257] that will impairs the transport of vesicles and synaptic components by both the anterograde and the retrograde transport [338].

4.4. Nitrotyrosination in Parkinson's disease

PD is one of the most prevalent neurodegenerative diseases. It affects to motor control producing rigidity, tremor, bradykinesia and postural instability. All these symptoms are caused by the death of 70% of dopaminergic neurons in the Substantia Nigra [339] due to the aggregation of the α-synuclein, which is a 140 kDa protein with a function in the trafficking and release of neurotransmitter vesicles [340,341]. Histopathologicaly PD is characterized by two main hallmarks: Lewy neurites and Lewy bodies. Lewy bodies are eosinophil inclusions, constituted mainly by α-synuclein [342]. Lewy neurites are accumulations of α-synuclein misfolded in amyloid structures in axons and neurites [343].

Under pathological conditions α-synuclein forms oligomers and later fibrils [344] however fibril formation is considered a mechanism of protection against oligomer neurotoxicity [345]. There is evidence of nitrotyrosination in the Lewy bodies from PD patients [346]. In particular the nitration of α-synuclein has been demonstrated in PD patients [347,348]. Nitration through tyrosine oxidation induces its aggregation [349], which will inhibit its ability to bind to the neurotransmitter vesicles.

The onset and progression of PD is also related with the nitrotyrosination of other proteins. Tyrosine hydroxylase is the key enzyme in cathecolamines synthesis from tyrosines and it is has been demonstrated that can be nitrotyrosinated impairing its catalytic activity [350] and therefore avoiding dopamine synthesis.

ONOO- has been shown to inhibit the presynaptic dopamine transporter [351], which mediates the uptake of dopamine from the synaptic cleft to stop dopamine signaling and to refill the dopamine vesicles. Its inactivation will induce a decrease in dopamine delivery.

Regarding parkin, a ligase that ubiquitinates proteins, it has been demonstrated it is S-nitrosylated and its S-nitrosylation produces a lack of function contributing to PD onset [112]. The pathophysiological consequences may be the impairment of the proteosomal degradation of misfolded proteins, the persistence of dysfunctional senescent mitochondria or the induction of increased mitophagia. Moreover PTEN-induced kinase 1 (PINK1), a mitochondrial serine/threonine-protein kinase that activates parkin, has been also demonstrated to be nitrated in pro-oxidant environments [352], that would contribute to the harmful effects of parkin S-nitrosylation.

5. Conclusions

NO is a molecule with pleiotropic effects in brain. NO favors synaptic functions by LTP maintenance and protein translation at dendritic spines. It is also critical to guarantee the proper blood supply to neurons and it has been demonstrated to be an antiapoptotic molecule and a regulator of neuronal function by nitrosylation. However, when NO is produced in a pro-oxidant environment, as during aging or in AD, reacts with $O_2\cdot^-$ producing ONOO-, which nitrotyrosinates proteins damaging brain cells. The physiological functions of NO are so critical for brain and vascular system that therapies aiming the direct regulation of its production will be harmful. However, the inhibition of free radical burst, the use of ONOO- scavengers or the stimulation of NO down-stream effects, such as the increase in cGMP levels or phosphodiesterase activity, will be more proper therapeutic approaches.

Competing interests

The authors declare that they have no competing interests that might be perceived to influence the results and discussion reported in this paper.

Transparency document

The Transparency document associated with this article can be found, in online version.

Authors' contributions

All authors have made equal intellectual contributions to the writing of this manuscript. All authors read and approved the final manuscript.

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