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Review

From birth to death: A role for reactive oxygen species in neuronal development

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ABSTRACT

Historically, ROS have been considered toxic molecules, especially when their intracellular concentration reaches high values. However, physiological levels of ROS support crucial cellular processes, acting as second messengers able to regulate intrinsic signaling pathways. Specifically, both the central and peripheral nervous systems are especially susceptible to changes in the redox state, developing either a defense or adaptive response depending on the concentration, source and duration of the pro-oxidative stimuli. In this review, we summarize classical and modern concepts regarding ROS physiology, with an emphasis on the role of the NADPH oxidase (NOX) complex, the main enzymatic and regulated source of ROS in the nervous system. We discuss how ROS and redox state contribute to neurogenesis, polarization and maturation of neurons, providing a context for the spatio-temporal conditions in which ROS modulate neural fate, discriminating between "oxidative distress", and "oxidative eustress". Finally, we present a brief discussion about the "physiological range of ROS concentration", and suggest that these values depend on several parameters, including cell type, developmental stage, and the source and type of pro-oxidative molecule.

Contents

1. Introduction

1.1. General overview of oxidative molecules

Reactive oxygen species (ROS) form a family of molecules derived from molecular oxygen (O_2) present in the atmosphere.

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The most common ROS members are the superoxide anion ($O_2^{\bullet-}$), the hydroxyl radical ($HO^{\bullet}$) and hydrogen peroxide (H_2O_2) [1]. Both superoxide anions and hydroxyl radicals are free radical molecules, with one electron missing from the atomic orbit of the oxygen molecule. In contrast, hydrogen peroxide is an electrically neutral molecule and is chemically more stable than the other ROS family members [2]. Altogether, ROS support the oxidative power of the eukaryotic cell, promoting important physiological functions, ranging from the innate immune response to neuronal development.

ROS are produced either enzymatically or non-enzymatically. The mitochondrion is one of the main sources of intracellular ROS, as a consequence of aerobic metabolism and ATP synthesis [1]. The contribution of mitochondria to the cellular concentration of ROS is notable, and several anti-oxidant systems within these organelles have been described in detail [3–6]. In addition, enzymatic ROS synthesis, mainly sustained by the NADPH-oxidase (NOX) family proteins, contributes towards maintaining physiological ROS levels according to cellular demands [7]. In fact, a recently published study supports the notion that NOX enzymes are instrumental in sustaining almost 45% of intracellular hydrogen peroxide in cultured hippocampal neurons, showing the strong influence that NOX enzymes have on the redox state [8].

Most of the literature discusses the disadvantages and benefits of O_2-dependent oxidation. Of note, molecular nitrogen (N_2), the most abundant gas in the troposphere, also drives the synthesis of pro-oxidative molecules, collectively named Nitrogen Reactive Species (NRS) [9]. Both the nature and functions of NRS have been less explored than those of ROS. Nevertheless, it is very likely that the contribution of NRS to neuronal physiology is important, as N_2 represents almost 78% of the air we breathe.

This review focuses on the neuronal effect of ROS synthesis mediated by the NOX complex, discussing their contribution to differentiation, development and regeneration of neurons of both the central and peripheral nervous systems.

1.2. ROS molecules in physiological and pathological signaling

In general terms, ROS have been considered for many years as toxic molecules, generated as unavoidable by-products of cellular metabolism [10], leading to the oxidation of cellular macromolecules such as membrane lipids, proteins and DNA [11]. ROS have been largely associated with oxidative distress, producing an imbalance between oxidative and reductive power, and thus modifying the redox status of the cell [2,12]. The list of diseases linked to oxidative stress is vast and includes several types of cancer [13], atherosclerosis, diabetes [14], and neurological disorders [15], like Amyotrophic Lateral Sclerosis and Parkinson's disease, among others [2]. Interestingly, many of these pathologies emerge with aging, which highlights the point that both oxidative stress and lifespan or health span may be connected, probably as a consequence of living in an aerobic environment. Undoubtedly, abnormally high and dysregulated ROS production leads to oxidative distress and cell death, but the regulation of ROS levels in response to cellular demands is critical for normal cell behavior.

Accumulating evidence suggests that ROS should be considered as second messengers involved in numerous signaling pathways in health and disease [9,16,17]. Indeed, ROS fulfill several criteria of second messenger molecules, such as a short life-time and the ability to amplify a cellular signal triggered by the primary ligand. In addition, ROS have the special attribute of "chemical interconversion" [18]. The superoxide anion derived from NOX enzymes is rapidly converted into hydrogen peroxide, either spontaneously or enzymatically by superoxide dismutase (SOD). In turn, hydrogen peroxide can be transformed into the hydroxyl radical *via* a non-enzymatic step called the "Fenton reaction", which mostly depends on the availability of Fe^{2+} in the cytoplasm [19]. Another feature of ROS, consistent with their role as possible second messengers, is that the synthesis of superoxide anions and hydrogen peroxide (but not hydroxyl radicals) is finely regulated [20–22].

2. The NOX complex: an enzymatic and regulated source of hydrogen peroxide in the nervous system

2.1. Structural and biochemical features of NOX enzymes

The main product of the NADPH-oxidase (NOX) enzymes is the superoxide anion. Nevertheless, superoxide dismutation (either spontaneously or enzimatically) leads to the synthesis of hydrogen peroxide, the more stable molecule of the ROS family [19]. In other words, NOXs maintain enzymatically intracellular levels of hydrogen peroxide, and together with mitochondria, sustain the oxidative power of the cell [7]. The NOX family is formed by 7 members, named NOX 1–5 and Duox 1–2. All these enzymes share structural homology and catalyze the conversion of O_2 into $O_2^{\bullet-}$, which is coupled to the transformation of NADPH into $NADP^+$ [23–26].

Several NOX isoforms have been found in the central nervous system, including NOX 1, 2 and 4 [27,28]. Table 1 summarizes the tissue- and cell-specific expression of NOX isoforms. NOX2, also called $gp91^{phox}$, is the best characterized member of this family. In brief, NOX2 is an enzyme of 50 kDa, although its apparent molecular weight varies according to its glycosylation state, which depends on the tissue, type and developmental stage of the neurons [26,29]. NOX2 interacts with the $p22^{phox}$ protein, a regulatory subunit that increases NOX2 stability. The NOX2/$p22^{phox}$ complex resides in the plasma membrane of neurons. In addition, $p22^{phox}$ interacts with $p47^{phox}$ through a proline-rich C-terminal domain of $p22^{phox}$. The protein $p47^{phox}$ is usually called the "organizer subunit" because it links the NOX2/$p22^{phox}$ complex with the following subunits; $p40^{phox}$, $p67^{phox}$ and the small Rho GTPase, Rac1 [27]. Once the cytoplasmic subunits reach the plasma membrane, the NOX complex is fully assembled. This event is crucial to sustain physiological levels of superoxide anion and, consequently, hydrogen peroxide, in response to cellular demands. For example, hippocampal neurons that ectopically express the mutant $p22^{phox}$ P156Q, which has a dominant negative effect on NOX2 activity, display up to a 45% reduction in baseline hydrogen peroxide levels, suggesting that it significantly regulates NOX activity [8]. In addition, both NMDA and sustained glutamatergic stimulation of hippocampal neurons activate NOX2, inducing cell toxicity due to abnormally high ROS accumulation [30,31]. Nonetheless, further research is required to unveil what other extracellular and intracellular ligands promote the assembly of the NOX complex in neurons and, probably more importantly, the cellular contexts that regulate such assembly.

2.2. Expression of NOX2 subunits in the nervous system

The NOX2/$p22^{phox}$ complex was first described in 1985 in neutrophils under the name of cytochrome b-245, a glycoprotein involved in the immune response [32]. Subsequently, subunits have been detected in many other tissues, such as cardiac cells, muscle fibers, and adipose tissue, including the central nervous system where it is widely expressed [27,28]. An early study by Mizuki et al. detected $p40^{phox}$ subunit mRNA in the hippocampus and cerebellum of the mouse brain [33]. Later on, both the cytoplasmic and membrane-associated NOX subunits were detected by immunodetection in neurons in the adult murine brain, distributed principally in the hippocampus, cortex, brain stem, amygdala, striatum, thalamus and cerebellum [34–36]. *In vitro*, the expression of NOX subunits has been detected in cultured cortical and hippocampal neurons [37], with a somatic and dendritic distribution

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Table 1
Distribution and expression of NOX enzymes and subunits in the nervous system.

	Tissue/cell type	NOX complex subunits	Expression stage	References
Central Nervous System (CNS)	Hippocampus	NOX1, NOX2, p22, p40, p47 and p67, NOX4	Development and adults; mice and rats. Tissue and primary neurons.	[4,29,30,33,36]
	Cortex	NOX1, NOX2, p22, p40, p47, p67, NOX4, NOX3.	Development and adults; mice and rats. Tissue and primary neurons.	[4,29,30,37]
	Cerebellum	NOX1, NOX2, NOX3, NOX4, p22, p40, p47, p67, NOXO1,	Development and adults; mice and rats. Tissue and primary neurons.	[30,33,38,43,]
	Purkinje cells	NOX2, p47.	Adults mice and rats. Tissue.	[36]
	Brainstem	gp91, p22, p40, p47, p67.	Adults mice. Tissue	[30]
	Dopaminergic cells	NOX1	Adults rats in substancia nigra. Tissue	[35]
	Astrocytes	NOX2, p22, p40, p47, p67, Rac.	Development and adults; mice and rats. Tissue and primary astrocytes. NOX1 expression not observed.	[35]
	Oligodendrocytes	N. D.	N.D.	
	Microglia	NOX2.	Adults mice and rats. Tissue and primary microglia. NOX1 expression not observed.	[35], [36]
Peripheral Nervous System (PNS)	Dorsal Root Ganglion	NOX1, NOX2, p22, p47, Rac1.	Development and adults; rats. Tissue and primary neurons.	[33,39,44]
	Sympathetic neurons.	NOX2, p22, p40, p47, p67	Development; rats. Primary neurons.	[36,37,39]
	Celiac ganglia	NOX1, NOX2, NOX4, p22, p47, Rac1	Development and adults; rats. Tissue and primary neurons.	[39,44]

[35]. Recently, NOX2, $p47^{phox}$, $p67^{phox}$ and $p22^{phox}$ subunits were detected in the hippocampus and cortex of embryonic rat brain homogenates (E18.5) as well as in immature cultured neurons, before polarization had occurred, suggesting that NOX-derived ROS are present during early neuronal development [8].

The NOX subunits are also expressed in the peripheral nervous system (PNS). The expression of the catalytic subunit NOX2 was first detected in dorsal root ganglion (DRG) neurons [38]. Later on, several other NOX subunits were detected in the PNS [39,40], including sympathetic neurons [41], superior cervical ganglion cells [42], cerebellar granule neurons [43], celiac ganglion cells and DRG neurons [44]. An example of the physiological contribution of ROS in axonal regeneration is supported by studies using the zebrafish model (*Danio rerio*) [45]. It has been shown that hydrogen peroxide promotes the re-innervation of the skin by somatosensory peripheral ending axons after cutaneous injury [45]. Of note, hydrogen peroxide production is not restricted to neurons, as Schwann cells are also a source of it and contribute to the recovery of damaged nerve tissue [46]. Similarly, a role for hydrogen peroxide during nervous system development in teleosts has been proposed in two recent papers. Weaver et al. reported that zebrafish express several NOX subunits at different developmental stages, leading to the hypothesis that NOX may contribute positively towards axonal pathfinding or outgrowth *in vivo* [47]. In addition, it was demonstrated that hydrogen peroxide production by NOX is essential for supporting the growth of retinal ganglion cells that have been produced locally by neurons [48]. Interestingly, the phenotype observed after NOX inhibition was overcome by the exogenous addition of hydrogen peroxide. Although a formal demonstration supporting a role for hydrogen peroxide and NOX functions in the PNS still remains elusive, we propose that similar mechanisms take place after damage in PNS nerves.

3. Contribution of the NOX complex and hydrogen peroxide synthesis to neuronal development

3.1. Role of the NOX-derived hydrogen peroxide in neurogenesis and neural stem cell maintenance

Brain development is an extremely complex process in which several signaling pathways are involved. In mice, cerebral cortex development is initiated by the onset of neurogenesis that occurs at days 11–13 of embryonic development, in which neural stem cells (NSCs), the multipotent stem cells of the developing central nervous system, simultaneously experience asymmetric divisions, migration from the subventricular zone to the apical cortex through the radial glia, and neural polarization, the process by which post-mitotic neurons develop the soma, the dendrites and the axon of the neuron [49].

The brain is especially sensitive to O_2 levels and oxidation for two main reasons. First, the brain has an elevated O_2 consumption rate in a very restricted space; it consumes almost 20% of the total O_2 required by the whole organism [50]. Second, high concentrations of Fe^{2+} have been found in the brain. Fe^{2+}, the active redox state of iron and the crucial reagent of the Fenton reaction, catalyzes the conversion of hydrogen peroxide into the hydroxyl radical, the most reactive and harmful ROS [19,51]. Accordingly, oxygen consumption in the brain is tightly linked with oxidation, and efficient mechanisms to maintain redox tone are required.

The NOX2 complex is expressed during brain embryogenesis [8,52]. Interestingly, both NOX2 and $p47^{phox}$ constitutive knock-out mice develop normal brains, without alterations in hippocampus development or cortex lamination, possibly due to partial functional compensation by other members of the NOX family [53]. In spite of this apparently mild phenotype, NOX2 knock-out mice exhibit a reduction in the levels of hippocampal neuronal progenitors in the adult brain [54], suggesting that basal ROS levels are instrumental in maintaining neurogenic niches.

Similarly, the tumor suppressor p53 protein tunes ROS levels in embryonic NSCs of murine brains, indicating that the redox state regulates their fate [55–58]. The $p53^{-/-}$ mouse presents elevated levels of ROS in the embryonic telencephalon (E11–13), triggering both a decrease in the number of neural precursors and the enrichment of cells expressing the post-mitotic neural markers doublecortin (Dcx) and β3-tubulin, suggesting that a pro-oxidant environment promotes neurogenesis, to the detriment of neural precursor maintenance [55]. In contrast, other authors have described that proliferative NSCs have elevated levels of ROS, even more so than other proliferative stem cells, such as the hematopoietic lineage [59,60]. In fact, NSCs cultured through the neurosphere assay, a culture method to clonally amplify NSCs [61–63], require relatively high levels of ROS to thrive properly [59]. Recently, an elegant study where oxygen tension was strictly controlled confirmed that ROS production is essential to promote the differentiation of NSCs into neurons. In the same study it was also demonstrated that such an effect was primarily dependent on NOX activity rather than

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mitochondria, emphasizing the idea that regulated sources of ROS production are well positioned to control fundamental aspects of brain functions [64]. In the same line of evidence, neurospheres treated with DPI, a pharmacological NOX inhibitor, decreased the proliferation rate of NSCs, which was rescued after treatment with hydrogen peroxide. Moreover, NOX 2 protein was detected in neurospheres, suggesting that NOX2-mediated hydrogen peroxide production strongly influences the proliferative ability of NSCs [59]. The authors also described that NOX2 maintains proliferative NSC through the modulation of the PI3K/Akt/mTOR pathway, a well-studied signaling mechanism involved in proliferation and cell survival.

Reducing endogenous ROS levels by using free radical-scavenging agents, significantly inhibits proliferation of neural precursors, whereas SIN-1, a peroxynitrite generator, promotes the proliferation activity of embryonic hippocampal-derived neural progenitor cells [65].

Accumulating evidence suggests that ROS modulate stem cell self-renewal and differentiation in their proliferative niches through complex signaling networks [66,67]. As discussed in Noble et al., precursor cells can be classified into two major categories depending on their response to the environmental redox state [68]. On one hand, cells that are slightly more reduced are more responsive to survival and proliferative stimuli. In contrast, precursors that exhibit a more oxidative state, respond better to differentiation stimuli, although these cells are more prone to trigger cell death mechanisms [68]. It is clear that the redox state strongly influences the balance between the proliferation and differentiation of neural precursors. However, further analyses are required to understand the mechanisms that control the spatio-temporal components that fine tune such redox balance.

3.2. Role of the NOX-derived hydrogen peroxide in early post-mitotic neuronal development and axonal growth

Neuronal development can be understood as the result of three sequential and inter-dependent events: 1) *neurogenesis*, which is the generation of new neurons as the result of the differentiation of NSCs [49], 2) *polarization* of post-mitotic neurons, a well-characterized 5-step process by which differentiated neurons develop two structurally and functionally different domains: the somato-dendritic and the axonal compartments [69–71], and 3) *maturation* of polarized neurons, when both axons and dendrites reach their final morphological and functional characteristics and are capable of establishing synapses [72].

Physiological hydrogen peroxide levels promote the establishment of neuronal polarity, neurite growth and axon specification of hippocampal neurons [8,52]. Upon NOX2 inhibition, neurons do not polarize properly and axonal specification is impaired. In contrast, a NOX2 gain-of-function induced by the over-expression of the cytoplasmic $p47^{phox}$ regulatory subunit, strongly enhances axonal growth, without causing cell death [52]. NOX-dependent neurite outgrowth has also been detected by other authors in primary cultured cerebellar granule cells [73], sensitive neurons of zebrafish [45] and bag cells of *Aplysia*, among others [74,75]. Fig. 1 summarizes the contribution of NOX-derived ROS on neurogenesis, polarization and maturation of neurons.

Both NOX2- and $p47^{phox}$-null mice present failure to develop spatial memory, a cognitive process associated with synaptic plasticity in the hippocampus [53]. In fact, these mice present abnormal long-term potentiation responses (LTP), a paradigmatic electrophysiology measurement that evaluates synaptic plasticity. Even though there were no apparent macroscopical alterations in the brain structure of NOX2-deficient mice, morphological microanalysis of the hippocampus was not performed. Given the influence of hydrogen peroxide on both neurogenesis and neuronal polarization, it is reasonable to hypothesize that neurons grown in a H_2O_2-deficient environment could be less developed than those neurons exposed to normal hydrogen peroxide levels. Interestingly, human patients with Chronic Granulomatous Disease (CGD), an infectious disease caused by deleterious mutations in NOX subunits, present cognitive problems during childhood [76]. Considering the difficulties in establishing a precise correlation between this phenotype and neuronal developmental failures, future research involving redox and cell biology will be required to shed light on this disease.

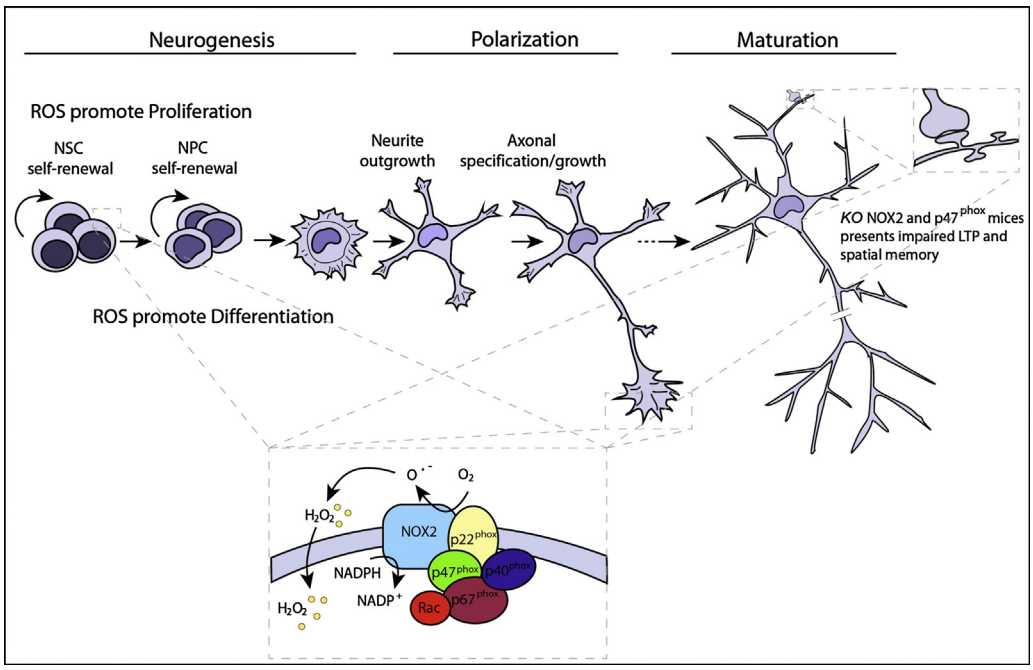

Fig. 1. NOX-derived ROS production contributes to neurogenesis, neuronal polarization and maturation. NOX2-mediated ROS production modulate both neural stem and neural progenitor cells self-renewal and maintenance. Later on, when neurons are differentiated it also modulate axonal outgrowth. In fully mature neurons, physiological NOX2-dependent ROS production is important to support LTP (synaptic plasticity) and maintain spatial memory.

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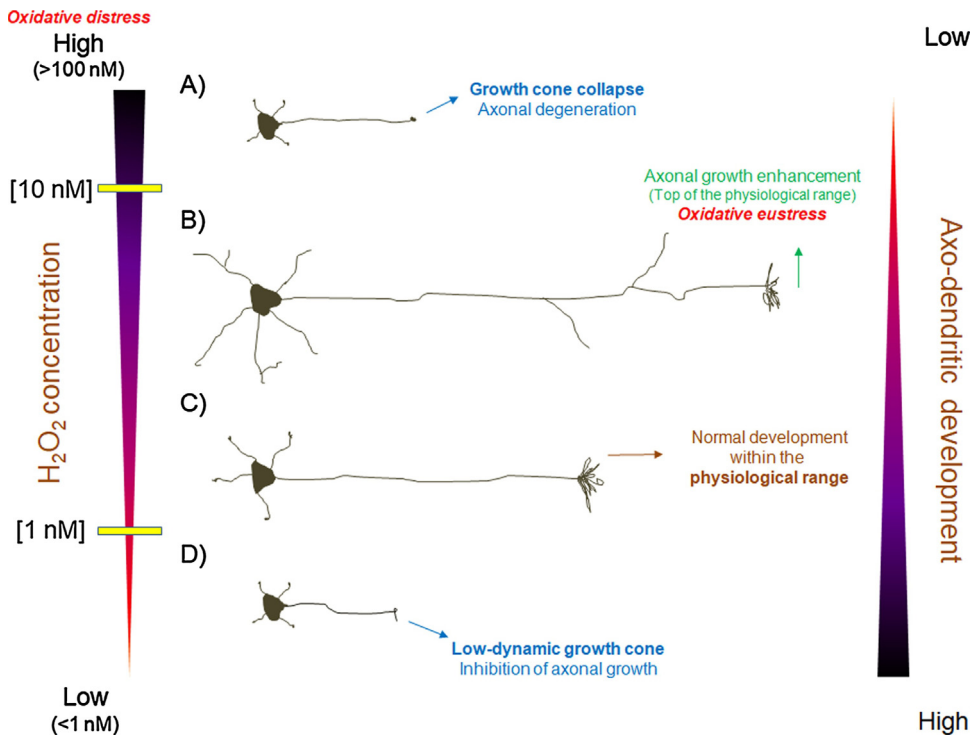

Fig. 2. Influence of the oxidative state on neuronal development. Hydrogen peroxide (H_2O_2), the most stable of ROS, drives either negative or positive outcomes for neuronal development depending on its concentration. A) Abnormally high and deregulated H_2O_2 production favors an oxidative distress condition, leading to the collapse of the axonal growth cone of neurons and subsequently axonal degeneration [18,82,83]. B–C) Elevated levels of ROS within the physiological range (10 nM) enhance neuronal development, promoting both axonal and dendritic growth [52] (B). Moderate to low H_2O_2 concentrations are instrumental for normal neuronal development, as well as axonal regeneration [8,45,73–75] (C). D) Abnormally low H_2O_2 concentration (by instance, below 1 nM), which may occur due to the loss of function of the NOX 2 complex, impairs both the polarization of hippocampal neurons and axonal growth, inhibiting neuronal development [8].

4. The good and evil faces of ROS in neuronal functions: a matter of concentration

For many years, the concept of "oxidative stress" (recently recalled "distress" in Sies, to reinforce the negative consequence of an imbalanced hydrogen peroxide synthesis [12]) has been used to highlight the presence and role of pro-oxidative molecules in biological systems. However, the mere detection of these molecules does not necessarily represent a stressful condition. In the above sections, we summarized several important physiological roles that hydrogen peroxide play in nerve cells, stressing the point that the accumulation of oxidative molecules, when it occurs within a physiological range, is instrumental for correct neuronal development and physiology. Nevertheless, alterations of the redox balance, leading to stressful conditions, undoubtedly affect the functions and viability of neurons. Several neurological disorders share the common characteristic of having elevated levels of ROS in neural and non-neural tissue [2]. For example, the amyloid-β (Aβ) peptide, the accumulation of which is directly associated with Alzheimer's disease, induces the formation of actin rods (actin-cofilin aggregations) through a NOX-dependent mechanism [77–81]. Actin rod formation could block vesicle trafficking at dendrites, decreasing the synaptic plasticity of mature hippocampal neurons. In addition to NOX-derived ROS, mitochondrial dysfunction also leads to an oxidative stressful condition, driving axonal degeneration.

Moreover, endogenous signaling molecules, such as glutamate or semaphorin3A (Sema3A), may generate neural damage depending on a spatio-temporal context [30,31,82,83]. For instance, glutamatergic excitotoxicity due to sustained glutamate stimulation, induces permanent activation of NOX2 in hippocampal neurons, leading to neural degeneration [30]. Along the same line, Sema3A, one of the most important repulsive guidance molecules, induces the collapse of the axonal growth cone through a H_2O_2-dependent mechanism in DRG cells and hippocampal neurons [82,83]. Both glutamate and Sema3A are good examples of how endogenous ligands may perturb the normal redox balance of neurons, compromising their integrity and function.

Fig. 2 summarizes the notion that, on one hand, high and sustained concentrations of ROS irreversibly alter the redox state of the neuron, compromising their functions and survival, whereas a well-balanced synthesis of ROS, especially hydrogen peroxide, within the physiological range, is required for the proper development and performance of the nervous system. An obvious and still un-answered question emerges: what ROS/hydrogen peroxide concentrations are considered within the physiological range? A major challenge at the cross-road of cell and redox biology has been measuring ROS both *in vitro* and *in vivo*. More challenging yet is to discriminate the chemical nature of the molecule studied. Currently, several ROS biosensors for detecting specific ROS based on fluorescence are available (either chemical or genetically-encoded), but most of them offer qualitative or semi-quantitative measurements [84,85]. Taking into consideration the evidence presented in this review, it is reasonable to propose that the "physiological ROS concentration" may be different for each cell type and may vary according to the developmental stage. Moreover, and considering the differences in reactivity between the superoxide anion, the hydroxyl radical and hydrogen peroxide, the physiological range is likely to be different for each type of ROS.

For the case of hydrogen peroxide, it has been recently suggested that its physiological range is between 1 and 10 nM [12]. Cells exposed to these concentrations would display "oxidative eustress", a concept used to describe the adaptive (beneficial) effect of ROS when they are present far below their toxic concentrations. In contrast, supra-physiological concentrations of hydrogen

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peroxide (above 100 nM) represent a harmful and oxidative stressful condition, defined as "oxidative distress". Clearly, the range between 10 and 100 nM is large, and it is not obvious what the cellular outcome would be within this range, especially considering cell type variability and spatio-temporal dependent regulatory mechanisms.

5. Final conclusions

This article summarizes the physiological and pathological contribution of ROS to neuronal development, including neurogenesis, polarization and maturation of neurons. It is important to make a clear difference between a stressful condition, where redox balance is lost and cellular homeostasis is compromised (here referred to as "oxidative distress") and "oxidative eustress", which refers to an adaptive response in conditions of physiological levels of hydrogen peroxide (the most stable and less aggressive of ROS), that impact positively on neuronal–and cellular–functions. The source, timing and localization of ROS synthesis are critical when evaluating the effects on neural physiology. Therefore, the development of additional sensitive ROS-specific probes for use at the cell scale is obligatory, in order to gain deeper insights into the cellular and subcellular roles of hydrogen peroxide and other ROS molecules. Finally, anti-oxidant therapies either for neurological disorders or non-neural pathologies, should consider the physiological range of ROS of each cell type, which will require the development of quantitative sensors to unveil the concentration range in which ROS behave as signaling molecules or toxic compounds.

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