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Review article

# 13 reasons why the brain is susceptible to oxidative stress

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A R T I C L E I N F O

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A B S T R A C T

The human brain consumes 20% of the total basal oxygen ($O_2$) budget to support ATP intensive neuronal activity. Without sufficient $O_2$ to support ATP demands, neuronal activity fails, such that, even transient ischemia is neurodegenerative. While the essentiality of $O_2$ to brain function is clear, how oxidative stress causes neurodegeneration is ambiguous. Ambiguity exists because many of the reasons why the brain is susceptible to oxidative stress remain obscure. Many are erroneously understood as the deleterious result of adventitious $O_2$ derived free radical and non-radical species generation. To understand how many reasons underpin oxidative stress, one must first re-cast free radical and non-radical species in a positive light because their deliberate generation enables the brain to achieve critical functions (e.g. synaptic plasticity) through redox signalling (i.e. positive functionality). Using free radicals and non-radical derivatives to signal sensitises the brain to oxidative stress when redox signalling goes awry (i.e. negative functionality). To advance mechanistic understanding, we rationalise 13 reasons why the brain is susceptible to oxidative stress. Key reasons include inter alia unsaturated lipid enrichment, mitochondria, calcium, glutamate, modest antioxidant defence, redox active transition metals and neurotransmitter auto-oxidation. We review RNA oxidation as an underappreciated cause of oxidative stress. The complex interplay between each reason dictates neuronal susceptibility to oxidative stress in a dynamic context and neural identity dependent manner. Our discourse sets the stage for investigators to interrogate the biochemical basis of oxidative stress in the brain in health and disease.

## 1. The brain and oxygen: locked in a lethal dance to the death

Despite weighing a mere ~1400 g the human brain voraciously consumes ~20% of the total basal oxygen ($O_2$) budget to power its ~86 billion neurons and their unfathomably complex connectome spanning trillions of synapses [1–3]—abetted by ~250–300 billion glia [4,5]. The brain must "breathe" to think—even transient ischemia heralds mass neurodegeneration [6]. Depriving the brain of $O_2$ for just 30 min in ischemic stroke exacts a devastating toll: every minute ~1.9 million neurons and ~14 million synapses perish [6]. Neurons and their synapses perish because without sufficient $O_2$, mitochondria are unable to reduce $O_2$ to $H_2O$ to support ATP synthesis [7]. Yet, perversely, at least *prima facia*, the brain carefully regulates $O_2$ use. For the simple biochemical reason that ground state molecular $O_2$ is a di-radical and, therefore, a potentially toxic mutagenic gas. Fortuitously, the potential oxidising power of $O_2$ is constrained by a chemical quirk: because the two lone electrons spin in parallel $O_2$ can only accept one electron at a time [8,9].

If spin restriction limits its reactivity, why is $O_2$ considered toxic? The answer lies in its ability to give rise to free radical and non-radicals, notably superoxide anion ($O_2^{\cdot -}$), hydrogen peroxide ($H_2O_2$) and hydroxyl (.OH) (their biochemistry is reviewed in [8,10,11]). Such species are usually considered to constitute the "dark side" of $O_2$ biochemistry—the unavoidable cost of using $O_2$ to respire [12]. It has long been assumed that their adventitious and unwanted generation sensitises the brain to "oxidative stress". Indeed, oxidative stress is intimately tied to neurodegeneration [13,14]. However, the simple dichotomy that $O_2$ is good and its reactive progeny (e.g. $O_2^{\cdot -}$) are bad, fails to explain why and how the brain is susceptible to oxidative stress because it is incorrect. To understand why and how the brain is susceptible to oxidative stress, one must abandon the dogma that $O_2$ derived free radicals and non-radicals are just deleterious metabolic by-products and consider their nuances. For example, nestled within the brains sensitivity to hypoxia, resides an extraordinary molecular detail: mitochondrial $O_2^{\cdot -}$ signals beneficial adaptive responses [7]. Far from being an exception, such redox signalling is pervasive [15,16]. Oxidative stress can arise when redox signalling goes awry (i.e. the "Janus" face of redox signalling). Redox nuances mean the brains susceptibility to oxidative

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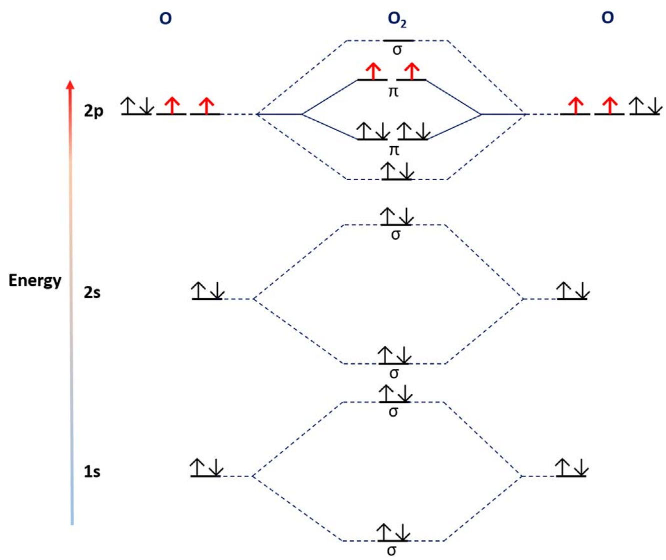


**Fig. 1.** ***Molecular diagram of a ground state diatomic oxygen molecule ($^3\Sigma_g^-O_2$).*** Left and right sides depict the electronic configuration of constituent oxygen atoms while the middle panel depicts bonding and antibonding orbitals within $^3\Sigma_g^-O_2$ by energy level. $^3\Sigma_g^-O_2$ is a di-radical because lone (i.e. single) electrons occupy the two degenerate $\pi^*_{2p}$ antibonding orbitals (shown in red). The two lone electrons possess parallel spins—locking $^3\Sigma_g^-O_2$ in a spin restricted state. Spin restriction is fortuitous because it constrains the reactivity of $^3\Sigma_g^-O_2$.

stress is seldom rationalised, which hinders attempts to disambiguate the complex relationship between oxidative stress and neurodegeneration. To advance mechanistic understanding, we biochemically rationalise 13 reasons why the brain is susceptible to oxidative stress. To do so, we draw on the seminal work of Barry Halliwell and John Gutteridge [17–19].

### 1.1. Redox signalling: reactive species play useful biological roles

A singular and indeed often overlooked reason why the brain is susceptible to oxidative stress is because reactive species play useful biological roles [19,20]. Two exemplars serve to illustrate the point. First, Chang's group [21] have shown that NADPH oxidase 2 (NOX2) derived $O_2^{\cdot-}$ and $H_2O_2$ regulate adult hippocampal progenitor cell growth via PI3K/Akt signalling. Their findings reveal a beneficial, homeostatic role for NOX2 derived $O_2^{\cdot-}/H_2O_2$ in the maintenance of essential neural progenitors [21]. The expression of NOX2, a dedicated $O_2^{\cdot-}$ producing enzyme [22,23], alone hints at an essential role for redox signalling. A related corollary is that NOX isoforms regulate hippocampal long term potentiation (LTP)—important for learning and memory [24]. Deleting NOX2 causes cognitive impairment in mice [25]. Second, Vriz's group, have identified beneficial roles for NOX derived $H_2O_2$ in axonal pathfinding and regeneration [26,27]. Axonal pathfinding wires the developing brain [28], in part, via secreted chemoattractant and chemo-repellent cues that ensure correct target innervation. Pharmacologically inhibiting NOX2 mediated $O_2^{\cdot-}/H_2O_2$ generation retards retinal ganglion cell axon outgrowth in vivo in larval zebrafish, placing $H_2O_2$ as an endogenous chemoattractant [26].

### 1.2. Calcium

Action potentials causes dramatic calcium ($Ca^{2+}$) fluxes in pre-synaptic terminals, raising $[Ca^{2+}]$ by ~four orders of magnitude (from 0.01 to ~100 μM [29]). $Ca^{2+}$ transients trigger neurotransmitter vesicle exocytosis [29]. Consequently, activity dependent $Ca^{2+}$ transients control bidirectional synaptic plasticity [30]. Bidirectional synaptic plasticity is fundamental to brain function—being required for learning and memory to give just one prominent example [31–33]. The brains reliance on $Ca^{2+}$ signalling [34] can cause oxidative stress: the nature of which is variable and context dependent owing to the complex relationship between $Ca^{2+}$ and the intracellular redox environment [19]. The interested reader is referred elsewhere for a comprehensive review of $Ca^{2+}$/ redox interplay [35], our discourse is confined to three points. First, $Ca^{2+}$ transients stimulate neuronal nitric oxide synthase (nNOS) mediated nitric oxide ($NO^{\cdot}$) synthesis [36], provided sufficient $O_2$ and NADPH are available for $NO^{\cdot}$ synthesis [37]. Residually elevated intracellular $[Ca^{2+}]$ may, therefore, increase $NO^{\cdot}$, which can inhibit mitochondrial respiration by binding to cytochrome c oxidase (COX) [38]. $NO^{\cdot}$ reacts at a diffusion controlled rate with $O_2^{\cdot-}$ to yield peroxynitrite ($ONOO^-$) [39]. $ONOO^-$ can lead to carbonate ($CO_3^{\cdot-}$) and nitrogen dioxide ($NO_2^{\cdot-}$) radical generation secondary to reaction with carbon dioxide ($CO_2$) to yield peroxomonocarbonate [40]. $CO_3^{\cdot-}$ and $NO_2^{\cdot-}$ may contribute to neurodegeneration—for example, by nitrating heat shock protein 90 to induce apoptosis in amyotrophic lateral sclerosis (ALS) [41]. A related corollary: $Ca^{2+}$ can increase phospholipase $A_2$ activity [34]. Phospholipase $A_2$ isoforms de-esterify membrane phospholipids—which can promote enzymatic (i.e. via LOX [42]) and non-enzymatic peroxidation of bis-allyic unsaturated lipids [43].

Second, intracellular $Ca^{2+}$ release—important for synaptic plasticity [44]—is redox regulated [45,46]. For example, Hajnoczky' group [47] show that mitochondrial $H_2O_2$ nanodomains regulate $Ca^{2+}$ transients. $Ca^{2+}$ transients induce endoplasmic reticulum (ER) mitochondria contacts, termed ER associated mitochondria membranes (MAM [48,49]), leading to mitochondrial $Ca^{2+}$ uptake. Mitochondrial $Ca^{2+}$ uptake amplifies ER $Ca^{2+}$ release by inducing potassium uptake to thereby increase matrix volume and compress the MIS to concentrate matrix $H_2O_2$ at the MAM [47]. These authors suggest $H_2O_2$ induces ER $Ca^{2+}$ release via the $IP_3$ receptor, consistent with its redox regulation via cysteine oxidation [50]. Because the MAM regulates a host of mitochondrial functions (e.g. transport and biogenesis [48]) one can easily envisage how dysregulated inter-organelle communication can cause aberrant local $Ca^{2+}/H_2O_2$ signalling associated oxidative stress [45]. To be sure, dysregulated MAM signalling is linked to neurodegeneration in AD and ALS [51]. For example, Stoica et al. [52] show that mutant TD43—a pathological trigger in ALS and frontotemporal dementia [53]—reduces MAM contacts and thereby disrupts $Ca^{2+}$ homeostasis. (Figs. 1–6)

A third related point of interplay: mitochondrial $Ca^{2+}$ overload opens the mitochondrial permeability transition pore (mPTP) [54]. mPTP opening induces $O_2^{\cdot-}/H_2O_2$ efflux and abolishes ATP synthesis [55–57]. Transient mPTP opening enables mitochondria to re-set matrix $Ca^{2+}$ [54,58], and is, perhaps, permissive for redox signalling by enabling $O_2^{\cdot-}/H_2O_2$ to exit mitochondria to evade matrix metabolism [59] (a phenomenon that may be linked to mitochondrial contractions [60,61]). Prolonged mPTP opening heralds necroptosis [62]. In addition, $Ca^{2+}$ overload can regulate intrinsic apoptosis. Importantly, necroptosis and apoptosis are linked to neurodegeneration [63,64]. Because mitochondrial $Ca^{2+}$ uptake supports ATP synthesis [65–67], decreased mitochondrial $[Ca^{2+}]$ may cause oxidative stress by increasing [NADH] and concomitant $O_2^{\cdot-}$ generation at the FMN site in complex I [68,69]. Cytochrome c could also use $H_2O_2$ to oxidise cardiolipin, an essential inner membrane phospholipid, to trigger intrinsic apoptosis [70,71]. Unsurprisingly (1) the brain expends considerable ATP to maintain intracellular $Ca^{2+}$ homeostasis and (2) neurodegenerative diseases are usually associated with disrupted $Ca^{2+}$ homeostasis.

### 1.3. Glutamate

Excessive glutamate uptake (e.g. by N-methyl-D-aspartate receptors (NMDARs)) causes excitotoxicity [72,73] secondary to aberrant $Ca^{2+}$ signalling—for example, leading to sustained calpain signalling [74]. Glutamate excitotoxicity leads to $Ca^{2+}$ overload linked mitochondrial [$O_2^{\cdot-}$/$H_2O_2$] release associated cell death, typically via apoptosis and necrosis [17,75,76]. $Ca^{2+}$ influx can activate nNOS: opening up the possibility that $NO^{\cdot}$ inhibits COX to increase mitochondrial [$O_2^{\cdot-}$/$H_2O_2$/$ONOO^-$]. Consistent with pharmacological nNOS blockade protecting against excitotoxicity [77]. Necrotic cell death amplifies excitotoxicity by elevating extracellular [glutamate] [78]. Intriguingly, NMDAR mediated glutamate uptake may be subject to differential spatial regulation: extra-synaptic uptake causes excitotoxicity whereas synaptic uptake initiates adaptive responses [79–82]. As Hardingham's group [79] show synaptic NMDAR mediated glutamergic neurotransmission up-regulates the peroxiredoxin-thioredoxin (PRDX-TRDX) enzyme system and down-regulates apoptotic signalling. Perhaps, spatial specificity underlies generator specific functionality wherein extra-synaptic NMDA linked mitochondrial $O_2^{\cdot-}$ generation is neurodegenerative whereas NOX2 linked synaptic NMDA receptor linked $O_2^{\cdot-}$ is protective [83]. Beyond receptors, glutamate can cause excitotoxicity by inhibiting the system $X_c^-$ transporter [84]—which exchanges intracellular glutamate for extracellular cystine [85]. Intracellular cystine is reduced to cysteine, which can be used by glutamate cysteine ligase for *de novo* glutathione (GSH) synthesis [86]. Inhibiting cystine uptake causes oxidative stress by depleting intracellular [GSH] [84,87]. Depleting intracellular [GSH] is sufficient to trigger ferroptosis—iron and lipid peroxidation dependent cell death [88]—suggesting extracellular glutamate is an endogenous ferroptotic cue [89,90]. However, as Cao & Dixon caution [90] despite redox commonalities glutamate excitotoxicity associated cell death and ferroptosis have distinctive elements, notably the involvement of apoptotic signalling in the former.

### 1.4. Glucose

The human brain consumes ~25% of circulating [glucose] to support neuronal activity [91] (corresponding to ~5.6 mg glucose per 100 g of brain tissue per min). The fate of glucose in the brain is complex and involves neuronal-glia metabolic coupling (reviewed in [3,92]). Glia metabolise glucose to lactate before it is taken up, converted to pyruvate and oxidised by neuronal mitochondria to generate ATP [3]. Consistent with evidence suggesting neurons efficiently metabolise lactate [93,94]. A related corollary: neurons constitutively degrade the rate-limiting glycolytic enzyme, phosphofructokinase (PFK), to preferentially use glucose to power the pentose phosphate pathway (PPP) [95]. From a redox perspective, transcellular metabolic coupling seems to compensate for the limited capacity of neurons to metabolise dicarbonyls owing to low glyoxylase 1 (GLO1) and glyoxylase 2 (GLO2) expression [96]. GLO isoforms metabolise methylglyoxyal (MG) [97]—a potentially toxic triose phosphate isomerase derived dicarbonly [98,99]—in a GSH dependent manner. GLO1 metabolises GSH conjugated MG (i.e. hemithioacetal) to S-D-lactoylglutathione before GLO2 converts S-D-lactoylglutathione to D-lactate and GSH. Low GLO isoform content coupled to comparatively low [GSH] sensitises neurons to MG toxicity: 250 μM MG is sufficient to saturate neuronal MG metabolism whereas astrocytic metabolism remains intact at 2 mM [96]. With the caveat that "free" [MG] is typically 2–4 μM [100]. Notwithstanding, MG is reactive—50,000 fold more so than glucose—and readily forms Shiff bases to glycate proteins, RNA and DNA [100]. In particular, protein glycation underlies the formation of advanced end glycation products (AGE), which can cause oxidative stress by stimulating inflammation via their receptor, impairing protein and mitochondrial function [100–102]. AGEs can arise in absence of high glycolytic rates because lipid peroxidation can yield MG [101]. In sum, the brain is susceptible to glucose induced oxidative stress [97].

### 1.5. Mitochondria

Disproportionate $O_2$ uptake supports oxidative phosphorylation to help fuel the brains extraordinary ATP demand [3]. Neurons expend ATP to maintain ionic gradients and support synaptic activity [103,104]. The sheer energetic costs of synaptic activity are exemplified by neurotransmitter loaded vesicle release alone consuming $1.64 \times 10^5$ ATP per second per vesicle [104,105]. Meeting neuronal ATP demands requires mitochondria, particularly synaptic mitochondria [106] owing to limited ATP diffusion. Neurons are especially reliant on mitochondria because they constitutively degrade PFK to limit glycolysis [95]—although glycosomes can temporarily support synaptic ATP synthesis [107]. Beyond oxidative phosphorylation, mitochondria are essential signalling hubs regulating a veritable plethora of essential processes, from $Ca^{2+}$ homeostasis, Fe-S cluster synthesis to cell fate [55,108,109]. Neuronal mitochondria are a quintessential double-edged sword: endowing neurons with ATP and signalosomes while imparting intrinsic neurodegenerative vulnerability to their dysfunction [110].

Instead of propounding the somewhat prosaic view that $O_2^{\cdot-}$/$H_2O_2$ are obligate, toxic by-products of mitochondrial respiration that cause oxidative damage, we interpret neuronal susceptibility to mitochondrial oxidative stress from a signalling perspective [111]. How mitochondria produce $O_2^{\cdot-}$/$H_2O_2$ (see Murphy [68] for a comprehensive review) places them as sentinels of organelle health [112]. Their *deliberate* generation is intimately tied to adaptive redox signalling [113]. Hypoxia signalling is a cogent example. Mitochondria sense hypoxia (i.e. 0.3–3% $O_2$) by generating complex I and complex III derived $O_2^{\cdot-}$/$H_2O_2$ to activate hypoxia inducible factor one alpha (HIF1-α) via degrading propyl hydroxylase. HIF1-α initiates adaptive transcriptional responses [114–118]. Because mitochondrial $O_2^{\cdot-}$/$H_2O_2$ production at a given site reflects: [$O_2$] [reduced site] and the kinetics of the reaction [68], hypoxia reduces complex I and III to trigger $O_2^{\cdot-}$ generation (which may be abetted by reduced COX activity to increase local $O_2$ availability). HIF1-α transcribes NDUFA4L2, an alternate complex I subunit, to suppress $O_2^{\cdot-}$ generation to conclude hypoxic signalling [119]. Aberrant redox signalling can be neurodegenerative. Failing to terminate mitochondrial $O_2^{\cdot-}$ generation could initiate redox regulated intrinsic apoptosis [120,121]. In addition, misassembled respiratory chains owing to mito-nuclear mismatch could induce the signal (i.e. $O_2^{\cdot-}$/$H_2O_2$) without the cue (i.e. hypoxia), leading to mal-adaptive responses [111]. If mutant mitochondria accumulate, they may cause dysfunction by clonal expanding their number because $O_2^{\cdot-}$/$H_2O_2$ regulate mitochondrial biogenesis [111,122,123].

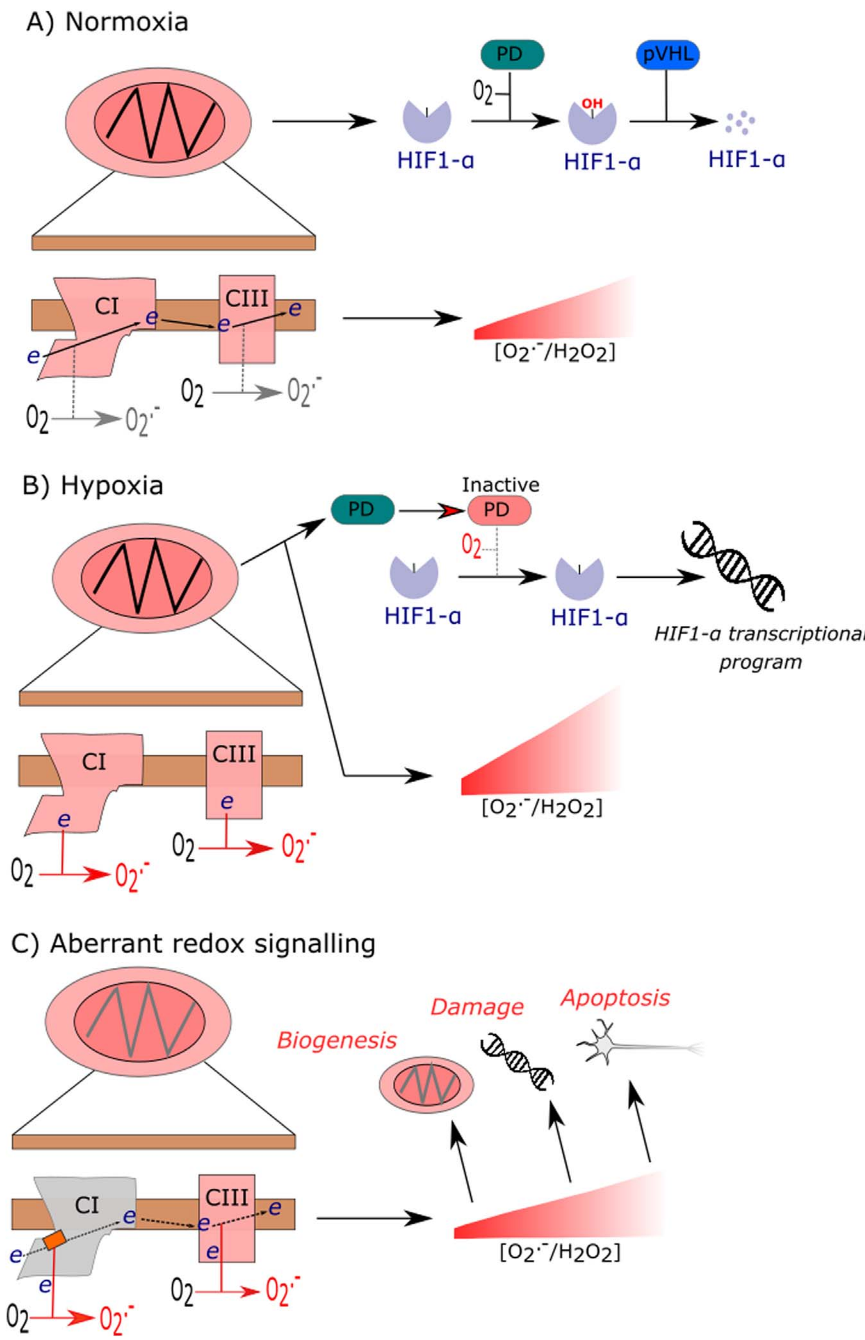


**Fig. 2.** ***Mitochondrial redox signalling***. A) In normoxia, mitochondrial $O_2^{\cdot-}$/$H_2O_2$ release is depicted as being low, based on the assumption that mitochondria are generating ATP. Electron flux through CI and CIII is depicted with minimal $O_2^{\cdot-}$ generation. PD uses $O_2$ to hydroxylate HIF1-α before pVHL degrades HIF1-α. B) In hypoxia, reduced CI and CIII generate $O_2^{\cdot-}$/$H_2O_2$. $O_2^{\cdot-}$/$H_2O_2$ inactivate PD, possible by liberating active site $Fe^{2+}$. PD inhibition enables HIF1-α to enter the nucleus to transcribe hypoxia associated gene programs. C) Aberrant redox signalling. A mis-assembled CI owing to mito-nuclear mismatch is depicted (i.e. grey box over CI). CI mismatch diverts electrons to $O_2$ to generate $O_2^{\cdot-}$. Various signalling abnormalities may ensue including biogenesis, DNA damage responses and apoptosis owing to persistent mitochondrial $O_2^{\cdot-}$ generation are graphically depicted.

### 1.6. Endogenous neurotransmitter metabolism generates hydrogen peroxide

Endogenous amine based neurotransmitter (e.g. dopamine) metabolism generates mitochondrial $H_2O_2$ via monoamine oxidase enzymes. Monoamine oxidase A (MOA-A) and B (MOA-B) catalyse a deamination reaction: amine + $O_2$ + $H_2O$ → aldehyde + $H_2O_2$ + $NH_3$. While both enzymes metabolise dopamine, tyramine, tryptamine and noradrenaline, MOA-A preferentially metabolises 5-hydroxytryptamine whereas MOA-B prefers 2-phenylethylamine [124,125]. During the catalytic cycle, amine oxidation to imine reduces a prosthetic flavin moiety, which reacts with $O_2$ to yield $H_2O_2$ [126,127]. Once the flavin is reduced, the rate of $O_2$ binding controls $H_2O_2$ generation, with the implication that [$O_2$] influences enzyme activity. The affinity of each isoform for $O_2$ is 10 and 240 μM for MOA-A and MOA-B, respectively [127]. Under $O_2$ saturated conditions, their capacity to produce $H_2O_2$ is considerable—Cadenas and colleagues [128] showed that tyramine demaination increases $H_2O_2$ levels by approximately 1 nmol/kg$^{-1}$/min$^{-1}$ in brain mitochondria. Axiomatically, the presence of a $H_2O_2$ generating enzyme together with neuronal activity induced substrate flux can cause oxidative stress [17,18]. Particularly, when one considers that MOA-B is localised to the outer face mitochondrial inner membrane [129] because little endogenous capacity to metabolise $H_2O_2$ in the mitochondrial intramembrane space (MIS) exists. Glutathione peroxidase 4 (GPX4), the sole peroxidase in the MIS [59], preferentially reduces lipid hydroperoxides (ROOH) over $H_2O_2$ [130,131]. MOA-A/B activity can trigger apoptosis in a $Ca^{2+}$ sensitive fashion [132–134], which may link MOA/B derived $H_2O_2$ and neuronal cell death. Unsurprisingly, aberrant MOA-A/B activity has been linked to ageing [135] and related neurodegenerative disorders, notably Alzheimer's disease (AD) and Parkinson's disease (PD) [136,137]. Spurring interest in the use of synthetic MOA-A/B inhibitors to treat neurodegeneration and indeed mood disorders [124,125,138].

An underappreciated aspect of MOA/B biology is by restricting $O_2^{\cdot-}$ induced neurotransmitter oxidation and subsequent redox cycling, they may limit $H_2O_2$ generation. For example, dopamine oxidation can yield multiple $H_2O_2$ molecules [139] whereas stoichiometric MOA-A/B metabolism produces a single $H_2O_2$ molecule. With the caveat that certain aldehydes products (e.g. 4-dihydroxyphenylacetaldehyde) can redox cycle [140,141]. A related corollary is that by helping to terminate neuronal activity MOA isoforms may protect against excitotoxicity. MOA-A/B may also protect the brain from exogenous xenobiotics. Notwithstanding, electrophilic aldehydes can conjugate macromolecules to cause damage [142]. For example, 3,4-dihydroxyphenylacetaldehyde, a dopamine metabolite readily conjugates proteins and is toxic to neurons [143]—a rise from 2–3 to 6 μM is sufficient to cause cell death [144]. MOA isoform activity must, therefore, be counter-balanced with aldehyde dehydrogenase (ADH) activity to prevent toxicity. Because ADH2 [145] is localised to the mitochondrial matrix the MIS may be unable to remove aldehydes enzymatically, which would favour macromolecule conjugates—especially if electrical charge occludes passive diffusion. Perhaps, electrophilic aldehydes, as opposed to $H_2O_2$, underlie MOA induced oxidative stress. While speculative, $H_2O_2$ signalling may inform the nucleus that aldehydes are being formed. ADH inhibition contributes to PD [146]—which underscores the importance of counter-balancing MOA activity. In sum, MOA isoforms can cause oxidative stress in the brain.

### 1.7. Neurotransmitters can auto-oxidise

In their seminal works, Cohen and Heikkla [147,148] showed that dopamine reacts with $O_2$ to generate a dopamine semiquinone radical, which can then react with another $O_2$ to generate $O_2^{\cdot-}$ and a dopamine quinone. While the initial rate of semiquinone radical formation is often slow [19], it can be accelerated by redox active transition metals [149]—which are abundant in the brain [17]. Dopamine quinones can combine to yield semiquinones [150]—which react with $O_2$ to give $O_2^{\cdot-}$, with the caveat that this reaction competes with a cyclisation reaction that averts redox cycling [151]. The mix of $O_2^{\cdot-}$, $H_2O_2$ and .OH detected is indicative of hydroquinone, semi-quinone and quinone equilibria [150]. Dopamine oxidation products can also redox cycle [152]. For example, 6-hydroxydopamine can be reduced to a semiquinone radical which reacts with $O_2$ to yield $O_2^{\cdot-}$, in turn, $O_2^{\cdot-}$ reacts with another 6-hydroxydopamine to regenerate the semiquinone radical and $H_2O_2$. A situation that leads to further $O_2^{\cdot-}$ generation [139] and .OH generation, provided a fraction of the $H_2O_2$ generated reacts with redox active transition metals [11]. Ubiquitous superoxide dismutase (SOD) isoforms [153–155] rapidly remove $O_2^{\cdot-}$ ($k$ ~$2 \times 10^9\ M^{-1}\ s^{-1}$) to terminate radical chains [156]. The net influence of SOD isoforms is complex because they can also favour $O_2^{\cdot-}$ generation [139,150]. By restricting $[O_2^{\cdot-}]$ to the picomolar range, SOD isoforms can shift equilibrium reactions of semiquinones towards their reaction with to $O_2$ to generate $O_2^{\cdot-}$; as is the case for 4-dihydroxyphenylacetaldehyde radical [140]. Importantly, serotonin and adrenaline also autoxidise, with adrenalin autoxidation being used to assay SOD activity [157]. Neurotransmitters with catechol groups, therefore, render the brain particularly sensitive to oxidative stress [17,18]. For example, redox cycling of dopamine metabolites, in particular 6-hydroxydopamine, contributes to PD [158,159]. In PD, dopamine oxidation [160] drives mitochondrial and lysosomal dysfunction, in part, via dopamine quinones abrogating glucocerebrosidase activity—a lysosomal enzyme implicated in PD pathogenesis [161]—and elevated mitochondrial $[H_2O_2]$.

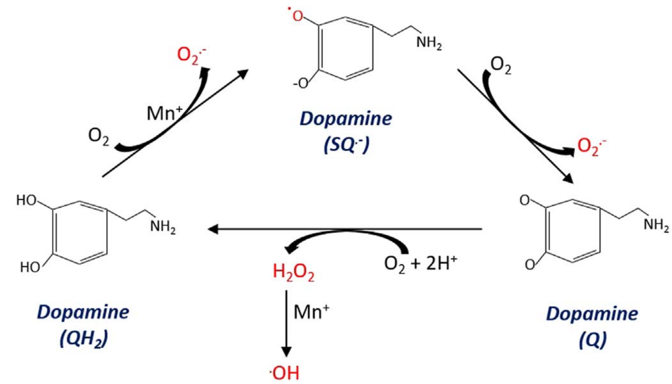


**Fig. 3.** ***Neurotransmitter autoxidation***. From left to right. A transition metal ($Mn^+$) catalysed reaction is shown wherein the alpha hydroxyl group of dopamine is oxidised to the semi-quinone radical. The semi-quinone radical then reacts with $O_2$ to generate $O_2^{\cdot-}$ and a quinone. $O_2$ can re-oxidise the quinone to quinol to generate $H_2O_2$. Transition metals may react with $H_2O_2$ to yield indiscriminately reactive .OH.

### 1.8. Modest endogenous antioxidant defence

As reviewed by Halliwell [17,18], modest endogenous antioxidant defence sensitises the brain to oxidative stress. That is, comparatively low endogenous antioxidant defence relative to many tissues (e.g. liver) makes the brain susceptible to disrupted redox homeostasis. While low catalase content—neurons possess 50 times lower catalase content compared to hepatocytes [162]—is a frequently cited exemplar [163], the relative importance of catalase to steady-state $H_2O_2$ removal is questionable. Aside from catalase being largely restricted to peroxisomes, its reaction mechanism requires two $H_2O_2$ molecules [164]—which may restrict its activity at nanomolar $H_2O_2$ [165]. GSH, however, provides a cogent example. Cytosolic GSH is ~50% lower in neurons compared with other cells (e.g. ~5 mM in neurons compared with 10–11 mM in hepatocytes). Low cytosolic GSH reflects, in part, a reduced capacity for GSH synthesis owing to low γ-GCL content—a corollary of minimal Nrf-2 content and activity [81,166]. Comparatively, low cytosolic GSH may restrict GPX4 activity [130], which may explain neuronal sensitivity to ferropotsis [167]. Low GSH may also limit the ability of neurons to metabolise electrophiles, particularly electrophilic aldehydes. From the discussion so far, it would seem the apparent defect relates to $H_2O_2$ metabolism [18,19] because SOD isoform content and activity is normative (i.e. no defect in $O_2^{\cdot-}$ metabolism). Intact $O_2^{\cdot-}$ metabolism (i.e. SOD activity) is essential because neurons are unable to survive genetic deletion of MnSOD [168–170], the mitochondrial isoform [154]. In sum, GSH linked enzymatic systems are modest in neurons.

In 1994, Soo Goo Rhee's group identified the PRDX family as ubiquitous cysteine dependent $H_2O_2$ peroxidases [171]. PRDX isoforms are reduced by TRDX, oxidised TRDX is, in turn, reduced by thioredoxin reductase at the expense of NADPH [172–176]. Their discovery has important implications for neuronal $H_2O_2$ metabolism because neurons express PRDX-TRDX isoforms [162,177]. A functional PRRX-TRDX system may enable neurons to metabolise $H_2O_2$—particularly when it is considered that PRDX isoforms are abundant and distributed throughout the cell [171,175,178]. We are unaware of any report to the effect that PRDX-TRDX activity is comparatively modest in neurons. On the contrary, PRDX activity may be comparatively high in neurons as they preferentially funnel glucose into the NADPH generating PPP [95]. However, enzymes (e.g. NOS) use NADPH to generate $O_2^{\cdot-}$ and $NO^{\cdot}$ [179,180], so it is unwise to assume NADPH exclusively fuels "antioxidants" [181]. However, PRDX6 prefers GSH as a reductant [182] so comparatively low GSH may limit its activity. It is remiss to consider PRDX-TRDX as "only" $H_2O_2$ "neutralisers" because compelling biochemical evidence suggests PRDX-TRDX transduce redox signals [16,172,183–187]. As Flohé et al. [188] elegantly enunciate nature is unlikely to have evolved over ten peroxidases just to remove $H_2O_2$. Lu, Holmgren and co-workers [162], suggest that PRDX-TRDX endow neurons with the capacity to harness their relative "oxidative stress" to transduce redox signals. If so, such a state of affairs is perilous, if PRDX isoforms become over-oxidised when [$H_2O_2$] rises to high nanomolar levels that seem to herald cell death [45,180]. Particularly, given the modest capacity of neuronal GSH linked enzyme systems [81,166]. PRDX-TRDX provide a means to remove, as well as, harness $H_2O_2$ for cell signalling but the possibility remains that beyond a critical threshold elevated [$H_2O_2$] easily short circuits this system to cause oxidative stress.

### 1.9. Microglia

Microglia are specialised, resident immune cells [189,190] that perpetually scan their local niche for homeostatic threats [191,192]. Microglia deploy extended processes to survey synapse health by monitoring neuronal activity [193]. By monitoring neuronal activity, microglia play an important role in removing unhealthy cells, neuronal wiring during development and activity dependent synaptic plasticity [194–197]. The ground breaking work of Bernard Babior [198], showed that active immune cells produce $O_2^{\cdot-}$ via NOX isoforms (principally NOX2 [23]). The role of $O_2^{\cdot-}$ in bacterial killing was one of the first examples of a biologically useful role for free radicals [199]. It is unsurprising, therefore, that microglia generate $O_2^{\cdot-}$ and related reactive progeny during phaogcytoysis [200]. However, one should note that because $O_2^{\cdot-}$ production depends on $O_2$, microglia activity will be extremely sensitive to local $O_2$ bioavailability—their $O_2$ use may even be one way to remove synapses by consuming $O_2$ to power $O_2^{\cdot-}$, as opposed to ATP, synthesis. It is unlikely that facile (e.g. .OH) or anionic species (i.e. $O_2^{\cdot-}$) exit phagocytic endosomes to harm neighbouring neurons (if anions did escape their entry is charge restricted in any event), uncharged $H_2O_2$ and $NO^{\cdot}$ may diffuse to cause damage or amplify local inflammation by attracting more microglia. Niethammer's and Amaya's groups have shown that $H_2O_2$ acts as a chemoattractant in wound healing and limb regeneration [201,202]. Patrolling microglia may "sense" $H_2O_2$ to induce their activation and proliferation [203], which provides a mechanism whereby neuronal $H_2O_2$ release attracts microglia. In support, Lyn, a tyrosine kinase, detects nerve derived $H_2O_2$ and primes microglia for chemotaxis via F-actin [204]. How Lyn detects $H_2O_2$ is unclear but may involve $H_2O_2$ linked phosphatase inactivation [15,16]. Self-amplifying inflammatory loops exist owing to cytokine and peroxidised lipid induced microglia activity [205,206]. While essential for normal brain development and function, unabated microglia activity can cause oxidative stress [206]. For example, in AD, microglia prune synapses to drive neurodegeneration [207,208]. Whether aberrant pruning requires oxidative stress is unclear., Perhaps peroxidised lipid metabolies [209](e.g. 4-HNE) attract microglia by modifying protein cysteine residues via Michael addition [210,211].

### 1.10. Redox active transition metals

Redox active transition metals (i.e. $Fe^{2+}$ and $Cu^{+}$) are enriched in the brain [17,18]. The relative abundance of transition metals in the brain is underlined by their 10,000 enrichment relative to neurotransmitters [212,213]. Chelated [$Fe^{2+}$] alone can reach mM levels. Nature harnesses the rich biochemistry of $Fe^{2+}$ and $Cu^{+}$ to accelerate chemical reactions. For example, $Fe^{2+}$ can bind electron dense O and N groups in organic molecules [214]. Accordingly, $Fe^{2+}$ (and $Fe^{3+}$) is required to ensure the catalytic activity of several enzymes, including aconitase, fumarase and cytochrome P450 [214]. In addition, $Fe^{2+}$ is essential for myelin synthesis [215,216] acting as a co-factor for essential *de novo* lipid synthesis enzymes. Neurons also harbour a loosely chelated Fe pool, termed the labile iron pool (LIP), which depending on dietary Fe intake is $\approx 20\,\mu M$ in most tissues [167,217]. Fe enrichment means neurons must tightly control [$O_2^{\cdot-}/H_2O_2$] to avoid the perils of mis-metallation—a corollary of FeS displacement [218]—and Fenton chemistry, which yields indiscriminately reactive .OH ($Fe^{2+} + H_2O_2 \rightarrow OH^- + .OH$) [19]. Even with abundant and kinetically rapid SOD enzymes maintaining steady-state [$O_2^{\cdot-}$] in the picomolar range, Imlay [219] estimates the half-time for mononuclear enzyme damage is still ~20 min owing to favourable kinetics ($k \sim 10^6\ M^{-1}\ s^{-1}$). For example, $Fe^{2+}$ loss inactivates the PPP enzyme ribulose-5-phosphate 3-epimerase [220]. Such inactivation may only be transient as compensatory mechanisms exist (e.g. $Mg^{2+}$ insertion, or LIP mediated re-metallation [220]). Notwithstanding, ablated PPP activity owing to ribulose-5-phosphate 3-epimerase inactivity could compromise neuronal function by restricting nucleotide synthesis [221]. Of particular interest, $Fe^{2+}$ regulates ferropotosis—a novel $Fe^{2+}$ and lipid peroxidation dependent form of cell death [88,167]. $Fe^{2+}$ contributes to ferroptosis by catalysing peroxyl (ROO.) and aloxyl (RO.) radical generation from ROOH in a reaction is kinetically favoured ($k \sim 1.3 \times 10^3\ M^{-1}\ s^{-1}$) compared to Fenton reaction($k \sim 76\ M^{-1}\ s^{-1}$) [19,222,223]. The influence of $Fe^{2+}$ is complex because $Fe^{2+}$ can inhibit lipid peroxidation by scavenging ROO. and RO. in kinetically faster reactions [222] (e.g. RO. + $H^+$ + $Fe^{2+}$ → ROH + $Fe^{3+}$, $k \sim 3.0 \times 10^8\ M^{-1}\ s^{-1}$). However, low [ROO./RO.] means $Fe^{2+}$ is more likely to react with ROOH. For these reasons, the brain is susceptible to dysregulated Fe homeostasis [224]. The pathological susceptibility of the brain to dysregulated $Fe^{2+}$ homeostasis is underscored by the observation that iron-amyloid beta complexes contribute to plaque deposits in AD [225].

Analogous to $Fe^{2+}$, neurons contain a "labile" $Cu^{+}$ pool [226] that seems to be important for cell signalling and neuronal excitability [227,228]. For example, neuronal activity redistributes the loosely chelated $Cu^{+}$ pool from the soma to dendrites, which regulates spontaneous neuronal activity [227,229,230]. In addition, $Cu^{+}$ is an essential co-factor for enzymes [212], prominent examples being COX and copper zinc SOD (CuZnSOD) [153,231,232]. Neuronal $Cu^{+}$ enrichment (0.1 mM, up to 1.3 mM in certain regions) predisposes to $Cu^{2+}$ catalysed Fenton chemistry and $H_2O_2$ assisted protein oxidation [212]. The potential perils of dysregulated $Cu^{+}$ homeostasis are exemplified in ALS. Specifically, mutated CuZnSOD variants contribute to both familial and sporadic ALS [233]. How CuZnSOD causes neurodegeneration is incompletely understood [234,235] but may relate to a toxic gain of function involving protein aggregates, peroxidase activity, which can generate $CO_3^{\cdot-}$ generation via $HOOCO_2$ [231,236], and thiol oxidase activity [237,238]. In addition, reduced CuZnSOD activity can also increase [$ONOO^-$] [239].

### 1.11. Unsaturated lipid enrichment

The brain is the major sink for polyunsaturated *n*-3 fatty acids [240], notably DHA. Given their ATP demands, one would expect neurons to oxidise lipids to generate ATP, particularly since the ATP yield is greater: 106 ATP per mol palmitic acid vs 32 ATP per mol glucose [241], and only 14–17 ATP per mol lactate [3]. However, compared with other metabolically active tissues (e.g. skeletal muscle [242]), beta oxidation is limited in the brain [241]. Perhaps, to conserve $O_2$—oxidising palmitc acid consumes 15% more $O_2$—and, in light of modest catalase activity [163], to limit preoxisomal enzyme induced $H_2O_2$ generation [243,244]. Recalcitrance to oxidising lipids to generate ATP may stem from using peroxidised lipids to signal [19]. For example, DHA can be metabolised to anti-inflammatory resolvins [245]. Beyond DHA, myelin synthesis requires fatty acids being enriched with cholesterol—its importance being reflected by the brain accounting for ~20% of total cholesterol [19]. Cholesterol auto-oxidises by free radical and non-radical mechanisms [246]. High unsaturated lipid content defines a cause of oxidative stress because of their susceptibility to lipid peroxidation and indeed may be the biological cost of using peroxidised lipids to signal [89].

Lipid peroxidation (reviewed in [43,247–250]) involves the initial generation of a carbon radical following an addition or abstraction reaction by a sufficiently reactive species (e.g. .OH) on a methylene group. As an aside, .OH may be dispensable for initiating lipid peroxidation, hyper-valent Fe-O species (e.g. FeIV = O) may be key [222]. Carbon radicals rapidly react with $O_2$ to yield ROO., which can abstract a bis-allyic $H^+$ from another methleyne group to propagate the radical chain by yielding ROOH and a carbon radical [43,247–250]. Alpha tocopherol (α-TOC) terminates radical chain propagation to yield ROOH and a resonance stabilised α-TOC radical [249]. ROOH can react with redox active transition metals to re-generate ROO. and RO. [222]. GPX4 rapidly removes ROOH to yield ROH [251], before the inactive

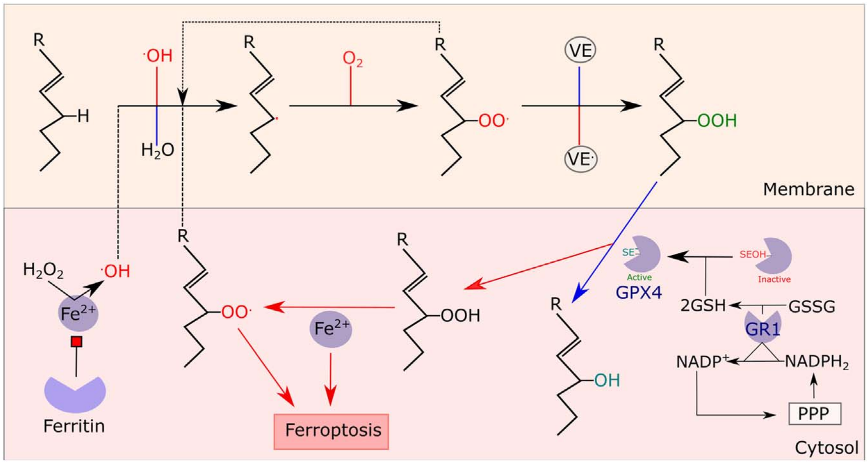


**Fig. 4.** ***Lipid peroxidation***. (1) Initiation..OH abstracts a $H^+$ from an unsaturated lipid to yield a carbon radical. (2) Oxygenation. $O_2$ reacts with the carbon radical to yield ROO. (3) Propagation. ROO. abstracts a $H^+$ from an unsaturated lipid to yield ROOH and a carbon radical. (4). Termination. Alpha tocopherol (VE) terminates chain radicals by reacting with ROO. to yield ROOH. (5). GPX4. GPX4 converts ROOH to the corresponding alcohol. GPX4 is regenerated by 2GSH and the resultant GSSG is reduced by GR using PPP derived NADPH. 6. $Fe^{2+}$. $Fe^{2+}$ reacts with ROOH to yield ROO.. ROO. can initiate lipid peroxidation, which triggers ferroptosis when GPX4 activity is suppressed. In addition, $Fe^{2+}$ can convert $H_2O_2$ to .OH (i.e. Fenton chemistry) to initiate lipid peroxidation. Ferritin can limit lipid peroxidation by ligating $Fe^{2+}$. Certain steps (e.g. carbon radical re-arrangement) are omitted for clarity.

enzyme is regenerated using GSH, which is, in turn, regenerated using NADPH dependent glutathione reductase [130,131,188]. Ferroptosis [90,252] explains why genetically deleting GPX4 is embryonically lethal [253,254] because GPX4 regulates ferroptosis by removing ROOH [223,255]—gain and loss of GPX activity is sufficient to disable and activate ferroptosis [256], respectively. Modest [GSH] may render neurons particularly susceptible to ferropotsis confirmed by the observation that conditionally deleting GPX4 is lethal to neurons [257–259]. Consistent with lipid peroxidation contributing to the pathogenesis of neurodegenerative diseases (e.g. AD [209,211]).

### 1.12. The brain uses NOS and NOX for signalling

The brain harnesses nNOS and NOX isoforms to achieve essential functions. First, nNOS uses $O_2$, NADPH and L-arginine to catalytically synthesise $NO^·$ [37]. The affinity of nNOS for $O_2$ is 300 μM, mean brain [$O_2$] is ~20 μM, which may limit $NO^·$ synthesis [260]. $NO^·$ regulates essential physiological processes, including LTP [261,262], axon growth [263] and pruning [264]. As discussed, $NO^·$ can underlie oxidative stress—especially when $O_2^{·-}$ is co-generated. nNOS biochemistry means that $O_2^{·-}$ and $NO^·$ can be spatially co-generated making [$ONOO^-$] generation likely [265]. Co-fluxes occur when nNOS is uncoupled. Uncoupling typically arises when essential co-factors (e.g. tetrahydrobiopterin) become oxidised or unbound. Second, NOX isoforms use prosthetic redox groups to oxidise NADPH to reduce $O_2$ to $O_2^{·-}$ [22,23]. NOX isoforms are important in the brain (reviewed in [266]) to support microglia and LTP to give just two examples [24]. Because NOX isoform mediated $O_2^{·-}$ generation is far from adventitious being regulated at several levels [22,23,267], NOX isoform associated oxidative stress likely stems from the unwanted and continued presence of activating cues coupled to a sustained supply of NADPH and $O_2$ to support enzyme activity. Such a scenario may manifest in neuronal inflammation [206] wherein cytokines provoke and sustain microglia NOX2 associated $O_2^{·-}$ generation [205].

### 1.13. RNA oxidation

RNA oxidation is a seldom appreciated reason why the brain is susceptible to oxidative stress [268]. Beyond essential messenger RNA, the brain heavily relies on non-coding RNAs, particularly long non-coding RNAs and microRNAs (reviewed in [269–271]). From a biochemical perspective, RNA is equally susceptible to oxidation as DNA, undergoing analogous reactions [272]. For example, 8-oxo-guanine is a principal outcome of both DNA and RNA oxidation [273]. Owing to its single-stranded nature, RNA is also vulnerable to oxidation and indeed alkylation [274] at Watson-Crick interfaces. RNA also lacks protective histones and nuclear compartment in axons and synapses. Although local protein synthesis is essential to synaptic function [275,276], the possibility that RNA oxidation perturbs local protein synthesis is unexplored. Oxidised RNA associated coding errors stall ribosomal protein synthesis [277], which can if left unrepaired produce truncated, mutated and mis-folded proteins [278]. The spatial positioning of mRNA close to mitochondria and the temporal dynamics of RNA oxidation (order of seconds) compared with translation (order of hours) make RNA oxidation likely—especially in neurons with divalent redox active transition metals present to catalyse Fenton chemistry [279–281]. The mandate to consider mRNA oxidation as a cause of oxidative stress associated neurodegeneration is strengthened by the observation that oxidised CuZnSOD mRNA is an early pre-clinical feature of ALS [282]. As a number of excellent reviews [268,272] surmise further work is required to understand oxidised RNA recognition, turnover and repair [283]. Only with a better understanding of each process can one appraise the neuronal susceptibility to RNA oxidation because [oxidised RNA] is a function of formation and removal over time.

## 2. Perspectives

We wish to propose an overarching perspective for interpreting why redox signalling leads to oxidative stress in the brain. The ultimate price of using redox signalling to inform brain function is innate susceptibility to oxidative stress when signals go awry—as seems to be the case in disease. Few neuroscientists would deny the central importance of neuronal activity. Based on how mitochondria produce $O_2^{·-}/H_2O_2$ [68], neuronal activity should divergently regulate mitochondrial $O_2^{·-}/H_2O_2$ generation. At an active synapse, ATP demands—provided they can be met—should reduce net mitochondrial $O_2^{·-}/H_2O_2$ generation. Whereas at an inactive synapse, low ATP demands and a reduced respiratory chain should favour mitochondrial $O_2^{·-}/H_2O_2$ generation, potentially placing mitochondrial $O_2^{·-}/H_2O_2$ as synaptic activity sentinels. If so, one can rationalise how synaptic inactivity induced mitochondrial $O_2^{·-}/H_2O_2$ release triggers long-term depotentation (LTD) and even synapse pruning—especially if the same pathway is used reiteratively [284]. Mitochondrial apoptosis regulates LTD and pruning [285–287]. Mitochondrial inactivity associated $O_2^{·-}/H_2O_2$ release may induce local sub-lethal intrinsic apoptosis to induct LTD and pruning. Perhaps, redox regulated apoptosis enables the developing brain to prune synapses—the essential prelude to a complex connectome and mandatory requirement for continued sculpting in adulthood [284]. Placing mitochondria with their hands on the proverbial shears renders the brain vulnerable to unwanted synapse loss. If mitochondria are unable to meet ATP demands or if $O_2$ is limiting resultant $O_2^{\cdot-}/H_2O_2$ release may recapitulate the "pruning" signal to cause unwanted synapse loss. Biological precedent exists: unwanted reactivation of developmental pruning signalling contributes to synapse loss in AD [207].

In biochemically rationalising 13 reasons why the brain is susceptible to oxidative stress, we deliberately adopted a global view focusing on "neurons" as a collective for the purposes of a general primer. Apt parallels between the monolithic umbrella terms neurons and reactive species exist [20]. Reactive species subsumes chemically heterogeneous species, that can differ in their rate of reaction with a given substance by orders of magnitude (e.g. for guanine .OH reacts at a diffusion controlled rate whereas $O_2^{\cdot-}$ leaves guanine unscathed owing to low reactivity). Analogous to reactive species, neurons are heterogeneous being ill-served by global monikers because they can widely differ in many key parameters, including function, location, connectivity, myelination and axon length. Neuronal heterogeneity informs differential susceptibility to oxidative stress both within a neuron (i.e. soma vs. synapse), subdomain (i.e. synaptic mitochondria vs. synaptic membranes) and between neuronal populations. Dopaminergic neurons in the substantia nigra pars compacta exemplify differential vulnerability: they experience residual (i.e. without additional homeostatic perturbation) oxidative stress because an L-type $Ca^{2+}$ channel defined mitochondrial $O_2^{\cdot-}/H_2O_2$ axis controls their autonomous pace-making capacity [288]. Teetering on the edge of an oxidative breakpoint, even minor unchecked shifts in the intracellular redox environment—perhaps related to dopamine metabolism [160]—seem sufficient to herald their demise.

Neuronal sensitivity to oxidative stress oscillates. Just as steady state $[O_2^{\cdot-}]$ reflects its *dynamic* rate of generation and removal in a given compartment [68], a myriad of interconnected factors dynamically set neuronal sensitivity to oxidative stress over time. We briefly consider $Fe^{2+}$ mediated ROOH reduction to ROO. as a topical example relevant to ferroptosis [223]. The second order bimolecular elementary reaction is informed by the rate constant, $[ROOH]_{ss}$ and $[Fe^{2+}]_{ss}$. Reactant availability at a given time governs the probability of ROO. generation—with GPX4 catalysed ROOH metabolism and ferritin mediated $Fe^{2+}$ chelation being prominent examples. If a xenobiotic conjugates GSH [19] to abrogate local [GSH] to compromise GPX4 activity, ROO. generation may be favoured. That the "history" of the neuron influences susceptibility to a redox challenge adds complexity. For example, synaptic activity associated sub-lethal redox challenges herald co-ordinated transcellular neuronal-glia adaptive responses that increase neuronal [GSH] (reviewed in [81]). In our example, an adapted neuron is better able to buffer the xenobiotic mediated GSH conjugation to abrogate ROO. generation to thereby raise the peroxidised lipid load required for ferroptosis [89]. As a cautionary note, adaption requires frequent stimulus because [GSH] is transcription dependent at multiple levels. An intriguing parallel with the exercise physiology axiom "*use it or lose it*" emerges: activity dependent beneficial adaptive redox responses persist with continued activity but progressively decay with inactivity.

From a translational perspective, the sheer complexity of neuronal redox homeostasis helps rationalise the failure of nutritional antioxidants to treat neurodegenerative diseases [289]. Bioavailability concerns aside, their failure relates to kinetic and spatial constraints (reviewed in [181,290–293]). The probability of any one compound possessing sufficient biochemical versatility to significantly modify each reason simultaneously is low. Above all, the failure of nutritional antioxidants reinforces their inherent biochemical strictures—being insufficient evidence to dismiss a causative role for oxidative stress. Much brain redox homeostasis in health and disease remains opaque. Only when basic research unmasks the mechanistic details can one rationally design redox active therapeutics for neurodegenerative diseases.

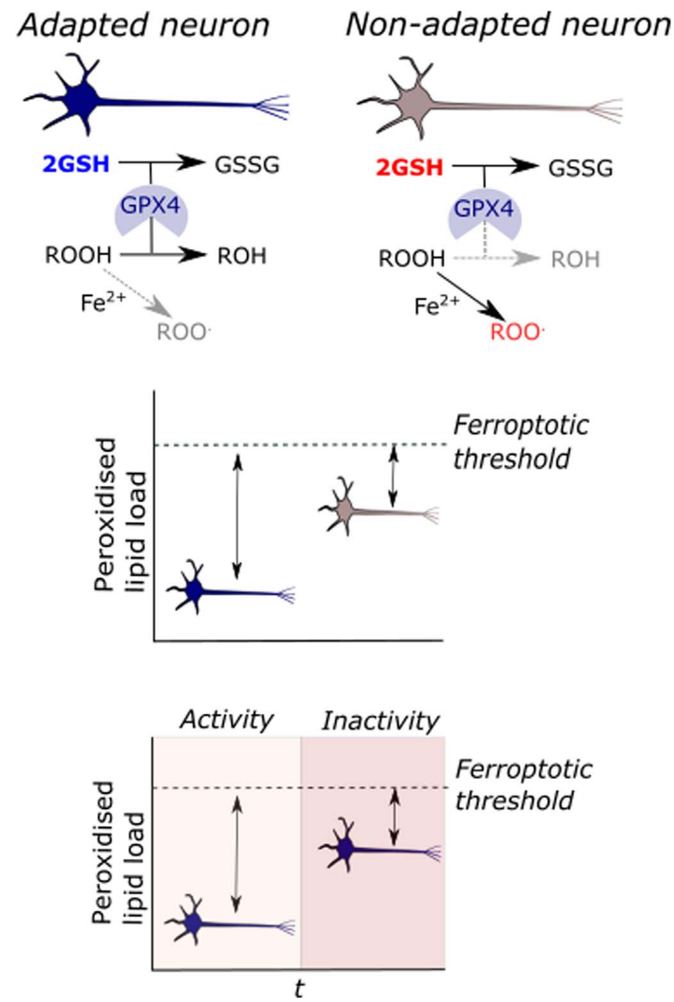


**Fig. 5.** ***Use it or lose it.*** (1) Depicts GSH-linked GPX4 ROOH metabolism in an adapted (left) and non-adapted neuron (right). Neuronal activity induced GSH up-regulation supports GPX4 activity to decrease [ROOH] to avert $Fe^{2+}$ catalysed radical reactions, which re-initiate lipid peroxidation. In the non-adapted neuron, low [GSH] increases the likelihood of $Fe^{2+}$ reacting with ROOH owing to decreased GPX4 activity. (2) A theoretical threshold model wherein the adaptive history (described above) divergently modulates the peroxidised lipid load required to induct ferroptosis. An adapted neuron, can withstand a larger absolute rise in [ROOH] before undergoing ferroptosis. (3) A theoretical threshold model an adapted neuron loses its ferroptotic resistance with persistent inactivity. Hence, a lack of stimulus (e.g. neuronal activity) erodes the adaptation.

## 3. Conclusion

A complex interconnected myriad of reasons render the brain susceptible to oxidative stress; just 13 (many more exist [17,18]) reasons include unsaturated lipid enrichment, glucose, mitochondria, calcium, glutamate, modest antioxidant defence, redox active transition metals, neurotransmitter auto-oxidation and RNA oxidation. The brain is susceptible to oxidative stress because it harness chemically diverse reactive species to perform heterogeneous signalling functions. From using lipid radicals to trigger ferroptosis when lipid signalling fails, $NO^{\cdot}$ to fine-tune synaptic plasticity or mitochondrial $O_2^{\cdot-}/H_2O_2$ to signal hypoxia. The balance between species specific useful and harmful biochemistry is a fine one, which, in the brain, means the relationship is bittersweet: exquisite redox signalling functionality easily gives rise to oxidative stress when electrons go awry.

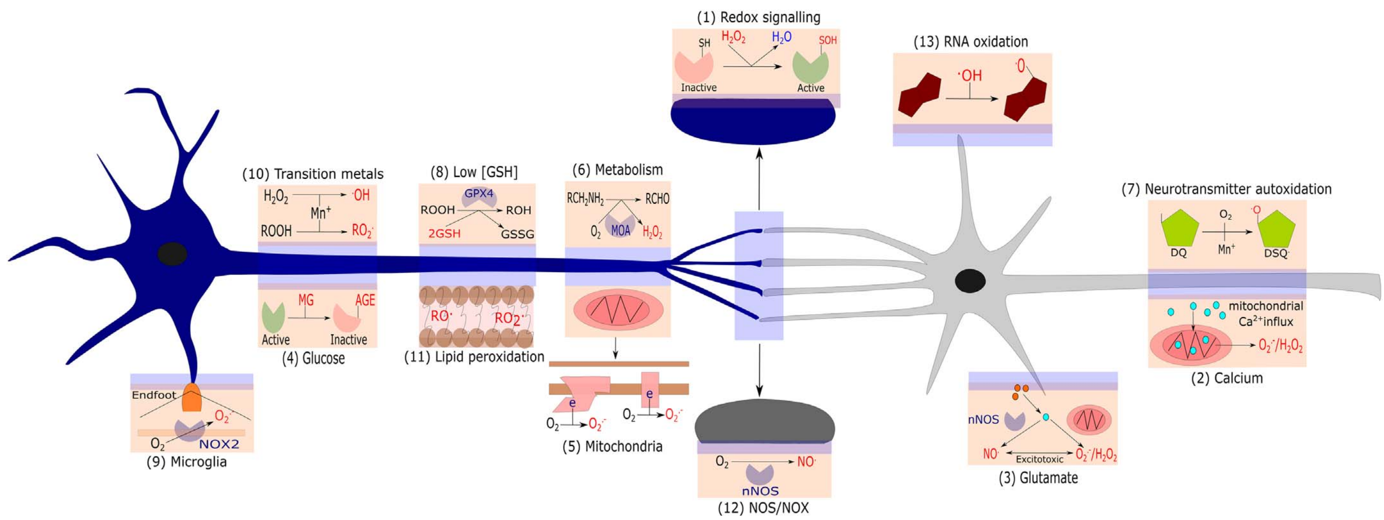


**Fig. 6.** ***13 reasons why the brain is susceptible to oxidative stress***. (1) Redox signalling. Depicts $H_2O_2$ induced activation of a signalling protein via sulphenic acid (SOH) formation. (2) Calcium. Depicts mitochondrial $Ca^{2+}$ overload induced $O_2^{\cdot-}/H_2O_2$ generation. (3) Glutamate. Depicts glutamate induced $Ca^{2+}$ release inducing nNOS mediated $NO^{\cdot}$ generation and mitochondrial $O_2^{\cdot-}/H_2O_2$ generation, leading to $ONOO^-$ and excitotoxicity. (4). Glucose. Depicts protein inactivation via AGE formation. (5). Mitochondria. Depicts mitochondrial $O_2^{\cdot-}$ generation at CI and CIII. (6) Metabolism. Depicts MOA isoform catalysed $H_2O_2$ generation. (7) Neurotransmitter oxidation. Depicts redox active transition metal ($Mn^+$) catalysed dopamine autooxidation to a semi-quinone radical. (8) Modest antioxidant defence. Depicts constrained GPX4 activity owing to low [GSH]. (9) Microglia. Depicts NOX2 mediated $O_2^{\cdot-}$ generation within an end-foot process. (10) Redox active transition metals. Depicts $Mn^+$ catalysed ROO. and .OH generation. (11) Lipid peroxidation. Depicts RO. and ROO. within a neuronal cell membrane. (12) NOS/NOX expression. Depicts nNOS mediated $NO^{\cdot}$ generation. (13). RNA oxidation. Depicts .OH mediated RNA oxidation (guanine is shown as an example).


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## Conflict of interest

The authors declare that no conflicts of interest exist.

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