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Review article

13 reasons why the brain is susceptible to oxidative stress

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ABSTRACT

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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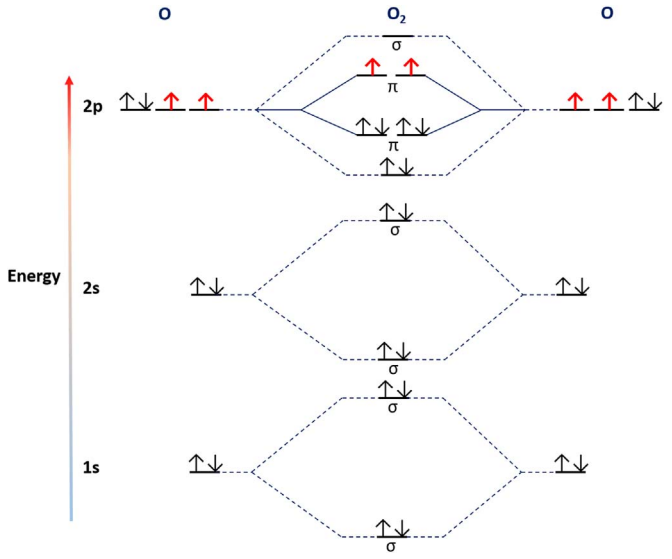

Fig. 1. ***Molecular diagram of a ground state diatomic oxygen molecule ($^3\Sigma_g^-O_2$).*** Left and right sides depict the electronic configuration of constituent oxygen atoms while the middle panel depicts bonding and antibonding orbitals within $^3\Sigma_g^-O_2$ by energy level. $^3\Sigma_g^-O_2$ is a di-radical because lone (i.e. single) electrons occupy the two degenerate π^*_{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