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Cysteine oxidation and redox signaling in dopaminergic neurons physiology and in Parkinson's disease

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Parkinson's disease (PD) is a neurological disorder affecting dopaminergic neurons in the nigrostriatal pathways of the brain. PD is a multifactorial disease and its causes should be sought in detrimental interactions between genes and environment. Since early mechanistic studies, excessive oxidation – or oxidative stress – emerged as a recurring and fundamental pathogenic mechanism, and consequently received significant attention. More recent evidence obtained at single-cell resolution, however, indicates that dopaminergic neurons in the substantia nigra display increased oxidation levels also in normal, physiological conditions; differently than pathological oxidation, the importance of this phenomenon is underappreciated. The nigrostriatal dopaminergic system is involved in behavioral strategies that have been under strong evolutionary pressure. It is therefore improbable that physiological oxidation in dopamine neurons is accidental. Here, we review recent literature to argue that moderate oxidation improves redox signaling – which in dopamine neurons is intertwined with electrophysiological activity and is important to regulate dopamine release – and also has a protective role. We also reason that physiological oxidation provides an example of antagonistic pleiotropy therefore offering an advantage during reproductive stages of life while becoming detrimental during aging. Collectively, we believe that these observations provide a new perspective in the biology of dopaminergic neurons and in PD.

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pathways of the brain. Dopaminergic loss displays anatomical specificity and is more pronounced the lateral ventral tier of the *substantia nigra pars compacta* (SNpc); dopamine neurons in the ventral tegmental area (VTA) are relatively spared [1]. PD etiopathogenesis is complex and stems from detrimental synergies between genetic and environmental factors, ultimately perturbing crucial processes in the cell. PD is largely sporadic and monogenic forms represent only 5% of total cases [2]. Studies on monogenic PD, however, have been instrumental to unravel pathogenic mechanisms. At present, PD has been associated with 19 loci, which in turn have been unambiguously assigned to 11 genes (PD genetics has been reviewed in several excellent articles, e.g. Ref. [3]). The latter are involved in different biological processes, from protein quality control to endocytic trafficking, to redox homeostasis, therefore reinforcing the complexity of PD etiopathogenesis.

Oxidation and PD

Despite the recognized intricacy of PD pathobiology, however, oxidative stress received continued attention since the seminal work of Langston *et al.* [4] describing parkinsonism in young subjects intoxicated with MPTP. Follow-up studies, in fact, demonstrated a direct inhibitory effect of MPTP on mitochondrial respiratory complex I with consequent increase in reactive oxygen species (ROS) production [5]. After its detection in patients' specimens, oxidative stress rapidly became regarded as a highly plausible PD mechanism [6,7]. Importantly, alterations in redox homeostasis have been detected in animal models harboring mutations in PD-associated genes [8]. Additionally, PD modeling largely relies on induction of oxidative stress and virtually all the accepted toxicological models are based on chemicals that ultimately function as pro-oxidants [9]. Oxidative stress, therefore, remains a recurrent factor of both genetic and idiopathic PD, and a point of convergence in the pathogenic cascade. More recently, the concept of oxidative stress in PD evolved in light of the crucial role of oxidation in normal biological function, where physiological alterations of the intracellular oxido-reductive (redox) state modify sensitive residues in proteins to modulate their activity [10]. The process largely operates via reversible oxidation of thiols in cysteine residues and is referred to as thiol redox signaling.

The topic of oxidative stress and redox signaling in neurodegeneration and in PD has been comprehensively reviewed in several and even very recent articles, and it is not our intention to revisit the information provided in

Parkinson's disease (PD) is a neurodegenerative disorder primarily affecting dopaminergic neurons in the nigrostriatal

these excellent publications [11–13]. We would rather like to emphasize few underappreciated aspects concerning the redox metabolism of dopaminergic neurons in normal conditions and the potential physiological consequences.

Oxidation and dopaminergic neurons

Dopaminergic neurons have distinctive redox properties. Here, a first supportive evidence comes from studies in toxicological models of PD, which clearly show that selective dopaminergic degeneration can be elicited not only by molecules specifically targeting dopaminergic neurons (e.g. MPTP), but also by chemicals acting systemically, for example rotenone and paraquat [14,15]. Another important evidence comes from studies that measure the intracellular redox state of dopaminergic neurons. Guzman *et al.* [16**] used a redox-sensitive green fluorescent protein (roGFP) [17] to demonstrate that in brain slices, in normal conditions (i.e. in the absence of pathology), dopamine neurons in the SNpc are more oxidized than those in the VTA. roGFP equilibrates – very slowly [18] – with the GSH/GSSG redox couple. Here, it should be emphasized that redox homeostasis relies also on additional couples, for instance thiols in thioredoxins [19,20], and that these systems are not at equilibrium, that is oxidation in one couple does not necessarily implies oxidation in the other [21]. Information inferred with roGFP is therefore necessarily limited to a specific aspect of the intracellular redox state. In a parallel approach, we took advantage of thiol-specific probes conjugated to fluorescent dyes to achieve differential labeling of oxidized and reduced cysteines to infer the global thiol/disulfide redox state in dopaminergic neurons at single cell level [22,23**]. Our experiments confirmed higher oxidation in dopaminergic neurons of the SNpc when compared to those of the VTA or to other neurochemical subtypes of neurons in the cortex [23**]. While the method we developed and used in these measures cannot discriminate between specific redox couples, it provides an overview of the general redox state of the cell. In combination with the results of Guzman *et al.*, our study provides converging evidence that the thiol/disulfide redox state is oxidized in dopaminergic neurons, in normal conditions, without ongoing pathology.

Which are the causes underlying increased oxidation?

Increased oxidation in the thiol/disulfide redox couple in dopaminergic neurons is consistent with other elements. Some evidence indicates that expression of ROS scavenging enzymes catalase, Cu/Zn SOD dismutase, and glutathione peroxidase is lower in the SNpc than in the VTA [24,25]. To refine those observations, we took advantage of publicly available datasets from transcriptomic studies performed at single-cell level [26] to explore the expression levels of key genes in redox

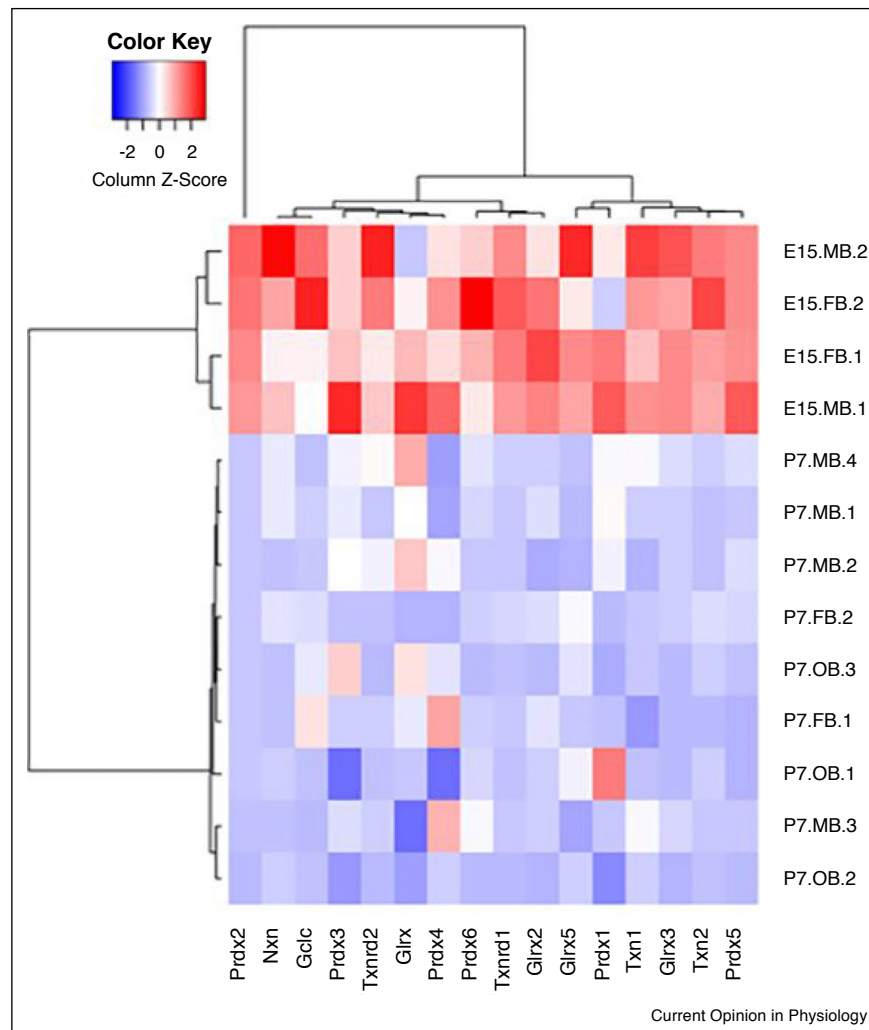
metabolism in embryos and seven days old mice. We found that expression of redox genes significantly decreases after birth; however, we could not detect major visible differences between dopaminergic neurons in the SNpc and those in the VTA (Figure 1). These data do not exclude differences, which could be detectable at protein level, but certainly suggest that there are no ostensible transcriptional differences in SNpc dopaminergic neurons.

The SNpc also contains high iron levels [27], which can induce oxidation, especially in combination with H₂O₂ via Fenton chemistry [6]. Because H₂O₂ is abundantly produced by the enzyme monoamine oxidase during dopamine degradation, dopaminergic neurons in the SNpc appear to be particular inclined to oxidation. Finally, high production of ROS has been also attributed to the distinctive electrophysiological properties of SNpc dopaminergic neurons. Some studies indicate that pacemaking activity (described below in the text) depends on calcium influx through voltage-dependent Cav1.3 channels, and that calcium is buffered by mitochondria, which in turn produce superoxide during the process [18,28*]. For sake of completeness, it should also be mentioned that other experiments attribute a less prominent role to calcium in dopamine neurons pacemaking activity especially in aging, which remains PD major risk factor [29,30]. Nonetheless, data generated independently, using different approaches, are consistent with the observation that the thiol/disulfide redox state in SNpc dopamine neurons is more oxidized than in other neuronal subtypes in normal conditions.

Oxidation and evolution

Unlike oxidative stress in PD, the concept that SNpc dopamine neurons display increased oxidation also in normal conditions has not received commensurate attention. Yet, this is an important issue because it is highly conceivable that a basal oxidized redox state underlies the particular vulnerability of SNpc dopamine neurons to pro-oxidants, therefore predisposing to PD pathogenesis. Here, it should also be emphasized that available evidence indicates that SNpc dopamine neurons do not put in place mechanisms to mitigate oxidation in normal conditions, as inferred from level previous literature and from transcriptomic analysis at single-cell level [26] of major redox genes (Figure 1). It is very unlikely that this distinctive biochemical characteristic is accidental. The dopamine system is in fact essential to adapt behavioral strategies to environmental stimuli: given an external input, it has a role in selecting the most appropriate motor program and in learning new advantageous schemes. Simply put, the dopamine system is crucial to learn how to discriminate between positive and negative stimuli, and what actions should be put in place to take advantage of beneficial situations while

Figure 1



Two-way cluster analysis of single cell next generation RNA sequencing data (GSE108020) [26] from embryonic (E15) and post-natal (p7) mice illustrating expression levels of major genes involved in redox metabolism. While expression of redox genes is clearly higher in embryonic neurons, in post-natal specimens no obvious differences can be appreciated between different areas, including between the SN (MB.4) and the VTA (MB.1).

Abbreviations for E15: FB.1: forebrain neuroblast; FB.2: post-mitotic forebrain tyrosine hydroxylase-positive (Th^+) neurons; MB.1: midbrain neuroblast; MB.2: post-mitotic midbrain DA neuron. **Abbreviations for P7:** FB.1: arcuate nucleus neuroendocrine Th^+ neurons; FB.2: mixture of arcuate nucleus Th^+ subtypes; MB.1: ventral tegmental area; MB.2: postnatal neuroblast; MB.3: periaqueductal gray area; MB.4: *substantia nigra*; OB.1: least mature Th^+ neurons; OB.2: progressively maturing Th^+ neurons; OB.3: most mature Th^+ neurons. **Genes abbreviations:** *Prdx1-6*: peroxiredoxin 1–6; *Nxn*: nucleoredoxin; *Gclc*: γ -glutamylcysteine synthetase, glutamate cysteine ligase; *Txnrd1-2*: thioredoxin reductase 1–2; *GlrX1-5*: glutaredoxin 1–5; *Txn1-2*: thioredoxin1–2.

avoiding dangerous ones [31,32*]. It is therefore obvious that the dopamine system has been under strong evolutionary pressure. The question is therefore why dopamine neurons evolved with a physiologically oxidized intracellular environment despite this feature poses risks for neurodegenerative diseases. Obviously, it is highly plausible that this question has multiple answers. One possibility, however, is that increased oxidation is functional for intense redox signaling, which is required in dopamine neurons in the SNpc to fulfil their physiological properties.

Physiology of DA neurons and redox signaling

Activity of dopaminergic neurons and subsequent regulation of dopamine release is a complex topic that has been reviewed in several excellent articles [31,32*,33]. For the purposes of this review, it is sufficient to provide a succinct overview of the process. Dopamine neurons display two dominant activity patterns (i.e. firing patterns), the tonic and the phasic modes. The tonic mode is characterized by spontaneous, regular activity that is associated with a steady level of dopamine, which is necessary to maintain normal function in the related

circuits [34,35]. In contrast, the phasic mode is characterized by sharp activity changes, that is bursts, that cause large changes in dopamine levels and may be initiated by different types of reward related stimuli [34–36]. The phasic mode is therefore highly relevant from the standpoint of the behavioral response. Among the various factors contributing to bursting control, at least by two types of ionic channels have a relevant role in the process: the ATP-sensitive potassium (K-ATP) channels and NMDA receptors, which can also act in concert to potentiate tonic firing [37,38**].

K-ATP channels are octameric complexes composed of four potassium inwardly rectifying channels (Kir6.X, typically Kir6.2 in neurons [39]) forming the pore, and four sulfonylurea receptor units (SUR1 or SUR2) that constitute the regulatory units [40]. Opening of K-ATP channels can be elicited by multiple factors associated with the metabolic status of the cell (reviewed in Ref. [41]) and causes membrane hyperpolarization, which in turn culminates in reduced electrical activity. This mechanism can serve as a neuroprotective strategy in conditions of metabolic distress such as hyperactivity during seizure [42,43] or excitotoxicity [44]. In SNc dopaminergic neurons, redox activation – for instance following H₂O₂ mediated opening of K-ATP – emerged as an important mechanism to regulate dopamine release [45**,46*]. The mechanism operates via modification of redox sensitive cysteine residues [47], is mediated by the regulatory subunit SUR1 [45**], and one study identified at least two-specific residues in the regulatory subunit SUR1 via site-directed mutagenesis [48]. Because expression of SUR1 has been associated with metabolic sensitivity and predisposition to dopaminergic degeneration, and in light of the distinctive redox properties of SNpc dopamine neurons, these findings are highly relevant for both dopamine neurons physiology and PD [49,50].

Also, NMDA receptors, which mediate calcium influx in the cell, can contribute to SNpc dopamine neurons' bursts in phasic mode. NMDA receptor activation alone, however, is not sufficient to switch neurons to the phasic mode and require other hyperpolarizing currents, for instance upon extrusion of sodium ions [51], or by K-ATP channel activation, which potentiate phasic burst firing [38**]. Also NMDA receptors are redox regulated and oxidation of sensitive cysteine residues inactivates the channel [52,53]. Thus, while both NMDA receptors and K-ATP channels sense the surrounding redox state, oxidation elicits opposite consequences. The physiological consequences of the different redox behavior of these channels will have to be addressed in future studies; however, the combination of redox mediated closure of NMDA receptor and K-ATP channel opening may prevent excitotoxicity while contrasting overexcitability, and may reflect a concerted strategy to protect against oxidative stress.

Thiol/disulfide redox state and H₂O₂ signaling

Collectively, the discussed findings highlight the relevance of H₂O₂ signaling for the physiology of SNpc dopaminergic neurons and its importance in governing behavioral aspects that have been highly exposed to evolutionary pressure (also discussed in Ref. [28*]). The question is whether increased intracellular oxidation in the thiol/disulfide network could be beneficial for this process.

The mechanics governing H₂O₂ redox signaling are complex and some of their aspects are only rudimentarily understood (reviewed in Ref. [54*]). It is for instance unclear how specificity is ensured in H₂O₂ signaling and in particular which chemical, biological, and structural criteria drive targeted modification of a certain cysteine residue. Another major issue stems from the very modest reactivity of protein thiols toward H₂O₂ ($k \sim 10^1\text{--}10^2 \text{ M}^{-1} \text{ s}^{-1}$) [55]. How can cysteine modification occur in a time frame compatible with neuronal physiological needs? It could be argued that the reaction efficiency would be highly improved in proximity of H₂O₂ sources, where local concentrations are particularly high. At least in the case of K-ATP channels, however, some evidence indicates that H₂O₂ signaling originates from mitochondria rather than plasma membrane proteins such as NADPH oxidase [46*], and proximity between H₂O₂ and its target is therefore questionable. Further complication arises from the far higher rate constants ($k \sim 10^5\text{--}10^8 \text{ M}^{-1} \text{ s}^{-1}$) of H₂O₂ scavenging enzymes – for instance peroxiredoxins (Prxs) – which are generally abundantly expressed. Very recent evidence suggests that Prxs might mediate H₂O₂ signaling to overcome low rates of reaction and lack of specificity [56**]; nonetheless, it cannot be excluded *a priori* that Prxs may quench, or even neutralize, H₂O₂ function as second messenger.

We hypothesize that constitutively higher oxidation in the thiol/disulfide couple could favor H₂O₂ at least in three ways. (1) Oxidation in a subpopulation of intracellular thiols would increase the relative concentration of H₂O₂, therefore favoring its action as a second messenger. This hypothesis implies that factors such as the *in vivo* redox potential of protein thiols will determine which residues will be oxidized in basal conditions, and also implies that proteins such as K-ATP channels will remain in a reduced state. Redox proteomic studies will be necessary to address this possibility. Additionally, experiments in which measures of redox signaling effectiveness will be paralleled by rigorous measures of intracellular redox state a single cell level will be necessary to conclusively assess the effect of dopaminergic neurons basal oxidation on H₂O₂ as second messenger. (2) Increased cysteine oxidation could also block the active site of Prxs, which are particularly sensitive to H₂O₂ mediated thiol oxidation, as also indicated by redox proteomics studies [57,58]. (3) Multiple lines of evidence indicate that

bioavailability of ROS is higher in SNpc dopaminergic neurons because of higher production and/or lower scavenging. In this chemical context, an increase in reversible cysteine oxidation may represent a protective strategy against irreversible and more dangerous forms of oxidation caused by high ROS levels. Accordingly, we have recently shown that moderate, reversible oxidation protects the dopaminergic system in multiple animal models of PD [59].

Are these observations important for PD?

Thiol/disulfide oxidation in normal conditions in SNpc dopamine neurons could be an example of antagonistic pleiotropy, that is a trait that is favorable during reproductive stages of life – for instance to improve novelty-induced exploration – and is therefore under evolutionary pressure, but becomes detrimental during aging [60,61]. Increased oxidation may provide the substrate for genetic and environmental factors to trigger dopaminergic degeneration. Moreover, some evidence indicates that moderate oxidation might be protective in PD and thus preservation of tolerable level of reversible cysteine oxidation may constitute an experimental therapy worth exploring.

Conflict of interest statement

Nothing declared.

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