HHS Public Access

Author manuscript

Biol Psychiatry. Author manuscript; available in PMC 2021 August 15.

Published in final edited form as:

Biol Psychiatry. 2020 August 15; 88(4): 326–336. doi:10.1016/j.biopsych.2020.03.016.

Potential Roles of Redox Dysregulation in the Development of Schizophrenia

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Abstract

Converging evidence implicates redox dysregulation as a pathological mechanism driving the emergence of psychosis. Increased oxidative damage and decreased capacity of intracellular redox modulatory systems are consistent findings in persons with schizophrenia as well as in persons at clinical high-risk who subsequently developed frank psychosis. Levels of glutathione, a key regulator of cellular redox status, are reduced in the medial prefrontal cortex, striatum and thalamus in schizophrenia. In humans with schizophrenia and in rodent models recapitulating various features of schizophrenia, redox dysregulation is linked to reductions of parvalbumin containing GABA interneurons and volumes of their perineuronal nets, white matter abnormalities and microglia activation. Importantly, the activity of transcription factors, kinases, and phosphatases regulating diverse aspects of neurodevelopment and synaptic plasticity vary according to cellular redox state. Molecules regulating interneuron function under redox control include N-methyl-D-aspartate receptor (NMDAR) subunits GluN1 and GluN2A as well as KEAP1 (regulator of transcription factor NRF2). In a rodent schizophrenia model characterized by impaired glutathione synthesis, the *Gclm* KO mouse, oxidative stress activated matrix metalloprotease 9 (MMP9) via its redox-responsive regulatory sites, causing a cascade of molecular events leading to microglia activation, perineural net degradation, and impaired NMDAR function. Molecular pathways under redox control are implicated in the etiopathology of schizophrenia and are attractive drug targets for individualized drug therapy trials in the contexts of prevention and treatment of psychosis.

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Disclosures: Dr. Perkins has served as a consultant for Sunovion and Alkermes, received grant support from Boehringer-Ingelheim, and been paid royalties from American Psychiatric Association Publishing. Dr. Do has received grant support from Boehringer-Ingelheim. Dr. Jeffries reported no biomedical financial interests or potential conflicts of interest.

Keywords

schizophrenia; psychosis; clinical high-risk; high-risk; oxidative stress; redox; glutathione; glutathione peroxidase; glutathione reductase; MMP9; perineuronal nets; PNN; parvalbumin; PVI; GABA interneurons; GSH; *Gclm* KO; *Grin2A* KO

Introduction

In excess, reactive oxygen (ROS) and nitrogen (RNS) species are deleterious by-products of aerobic respiration, causing oxidative damage to lipids, proteins, and nucleic acids. Importantly, the activity of many regulatory proteins is determined by whether thiol groups are reduced or oxidized ("redox state"). Broadly, homeostatic levels of ROS and RNS are required to control the activity of numerous transcription factors, kinases, phosphatases, and other molecules involved in neurodevelopment, synaptic plasticity, and many other functions [reviewed in (1)].

Oxidative stress is a pathological condition defined by a shift in redox balance from physiologic to pro-oxidant, indicating failure of compensatory molecular pathways to modulate cellular redox state resulting in oxidative damage. Increased oxidative damage and decreased capacity of intracellular redox modulatory systems are consistent findings in persons with schizophrenia, including persons who have never received antipsychotic medications [reviewed in (2)] and persons meeting clinical psychosis high-risk criteria who subsequently developed frank psychosis (3, 4). Furthermore, a common feature of diverse rodent models recapitulating various brain and behavioral abnormalities relevant to schizophrenia is redox dysregulation (5, 6). In this review we provide selected background information regarding physiologic redox regulation, summarize key aspects of schizophrenia neuropathology together with the evidence linking these findings to redox dysregulation, and discuss implications for the development of preventative interventions.

Background: Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS)

Figure 1 illustrates three critical functions of glutathione in maintenance of cellular homeostasis. One role is to prevent irreversible oxidative damage to lipids, proteins, and nucleic acids. Another is participation in the reduction and removal of oxidatively damaged molecules in reactions catalyzed by glutathione-S-transferase; a process that may deplete glutathione reserves. A third is to modulate functions of regulatory proteins and transmembrane ionic signaling [reviewed in (7)]. Glutathione and enzymatically generated ROS [O^{-}_{2}, H_2O_2, nitric oxide ($^{\bullet}NO$)] act on redox-sensing "thiol switches" in reversible reactions producing disulfide bonds, S-glutathionylation, sulfenic acid, nitric oxide derivatives, or other molecular changes. Such redox-mediated changes affect the conformational structure and thus the bioactivities of these molecules. Importantly, subcellular compartmentalization of ROS and antioxidant enzymes enables their local regulation of redox-sensitive proteins.

Cellular, Anatomical, and Circuit Alterations in Schizophrenia

Schizophrenia involves dysregulation of dopaminergic and glutamatergic brain circuitry [reviewed in (8)]. The dopamine hypothesis emerged from observations that dopamine antagonists lessen psychotic symptoms in patients with schizophrenia. Brain imaging studies converge on increased dorsal striatal dopaminergic activity as a core feature of schizophrenia [reviewed in (8)]. Furthermore, dopaminergic abnormalities precede the onset of schizophrenia as striatal dopamine activity was increased in persons at clinical high risk for psychosis and elevations predicted conversion to psychosis (9–13). Dopamine dysregulation is hypothesized to be a consequence of reduced activity of NMDA receptors (NMDAR) on inhibitory GABA interneurons. The NMDAR hypofunction hypothesis arose from studies in healthy humans demonstrating that NMDAR antagonists such as ketamine or phencyclidine transiently induced features characteristic of schizophrenia, including psychosis, negative symptoms, cognitive impairments, and altered evoked response potential (ERP) amplitudes including reduced mismatch negativity and P300 responses [reviewed in (14)]. Furthermore, both mismatch negativity and P300 impairments were apparent in clinical high-risk subjects and deficits predicted transition from high-risk to psychosis, implying NMDAR hypofunction preceded psychosis onset (15–19).

Subtypes of GABA interneurons with different roles in regulating excitatory/inhibitory balance and neuronal circuit synchrony have been identified [reviewed in (20)]. Post-mortem schizophrenia studies revealed widespread reductions of subtypes expressing somatostatin and parvalbumin in dorsolateral prefrontal, anterior cingulate, primary motor, and primary visual cortices, the hippocampus and thalamic reticular nucleus (21–27). One group reported reductions in somatostatin but not parvalbumin interneurons in the amygdala (28, 29). Thus, both somatostatin and parvalbumin interneurons are implicated in schizophrenia.

Neuronal circuit synchrony detected by EEG as electrical oscillations occurs at different frequencies. Somatostatin interneurons generate theta band oscillations. Mismatch negativity and P300 responses are detected within the theta band [reviewed in (30)]. P300 responses are also detected within delta band oscillations (31). In contrast parvalbumin-expressing interneurons generate high-frequency gamma oscillations (32). As reviewed by Reilly and colleagues (33), impairments on various gamma-band EEG paradigms were reported by most clinical high-risk, first episode and chronic schizophrenia studies, however longitudinal clinical high-risk studies reported mixed results (34–36).

Schizophrenia is characterized by widespread reductions in cortical and subcortical gray matter volumes (37–39), alterations in white matter integrity (40, 41), and functional dysconnectivity (42). Emergence of psychosis in clinical high-risk subjects was associated with accelerated loss of gray matter volumes involving prefrontal, parietal, superior temporal, and hippocampal regions (43–47) and cerebello-thalamo-cortical dysconnectivity (48–50). These brain regions overlap with regions involved in mismatch negativity generation (auditory cortex and less consistently inferior frontal cortical regions) (51, 52), P300 (widespread parietal and frontal cortical regions) (53, 54), and auditory evoked gamma band response (auditory cortex and medial cortical regions especially the anterior cingulate cortex) (55). Interestingly, one study reported clinical high risk subjects had deficits in

auditory gamma band response evoked by a demanding cognitive task that on simultaneous fMRI involved bilateral auditory, anterior cingulate, and dorsolateral prefrontal cortices and the thalamus (56).

Schizophrenia post-mortem studies found gray matter changes involved reductions in neuropil (57–59) and perineuronal nets (26, 29, 60, 61). Perineuronal nets are dynamic extracellular matrix structures, regulating neuronal synchronization, protecting parvalbumin interneurons from oxidative stress and inhibiting excessive plasticity [reviewed in (62)]. Importantly, as maturational critical periods close, neural networks involving parvalbumin interneurons become stabilized by perineuronal nets (61). Perineuronal nets play critical roles in protecting synaptic spines from pruning [reviewed in (63)], thus perineuronal net reductions may also be implicated in neuropil loss. In schizophrenia, evidence of mitochondrial dysfunction includes alteration of network morphology and activity of mitochondrial complex I (64). Postmortem studies also reported increased microglia density and indicators of microglia activation [metanalysis in (65)]. Microglia are brain-specific macrophages with diverse functions including regulation of synaptic plasticity by pruning synapses in an activity-dependent manner [reviewed in (66)].

Vulnerability of Parvalbumin Interneurons, Perineuronal Nets, and Oligodendrocytes to Oxidative Stress

Parvalbumin interneurons form networks of inhibitory GABAergic synapses contributing to excitatory-inhibitory balance and correlating signals among brain regions (67). To support high-frequency neuronal synchronization, fast-spiking parvalbumin interneurons are energy-demanding and thus as a corollary subject to high ROS production (68). Consequently, parvalbumin interneurons need well-regulated antioxidant systems to neutralize ROS and are vulnerable to redox dysregulation, whether induced by a compromised antioxidant system or ROS accumulation. Perineuronal nets protect parvalbumin interneurons from ROS, but excessive oxidative stress results in their loss (69). Microglia activated by oxidants, cytokines, or extracellular glutamate increase their phagocytic activity including synaptic pruning and release of ROS and other molecules that contribute to perineuronal net degradation (70). Oligodendrocytes are also vulnerable to oxidative stress, especially as their precursor cells mature and generate myelin [reviewed in (71)]. In particular, during neurodevelopment, the proliferation and differentiation of oligodendrocyte precursor cells as well as myelin maturation are dependent on redox status [reviewed in (72–74)].

The glutathione system plays a pivotal role in controlling parvalbumin interneuron redox status [reviewed in (75)]. Glutathione is a tripeptide made up of cysteine, glutamate, and glycine and is synthesized in two major steps (see Figure 1.4). The first step, combining cysteine and glutamate, is rate-limiting; homeostatic levels of glutathione are maintained by availability of cysteine as well as transcriptional control of the enzyme catalyzing this reaction, glutamate-cysteine ligase. Parvalbumin interneurons' supply of cysteine is linked to their activity and is regulated by astrocytes, thus, glutathione supply must match parvalbumin interneuron demand in order to maintain physiologic redox status (76).

A major regulator of cytoprotective responses to stresses caused by ROS and electrophiles is the KEAP1/NRF2 pathway. Under normal conditions the transcription factor NRF2 is repressed by KEAP1. Under oxidative stress NRF2 becomes derepressed, translocates to the nucleus, binds to antioxidant response elements (ARE) in DNA promotor regions, activating transcription of numerous genes including glutamate-cysteine ligase [reviewed in (77)]. Interestingly, KEAP1 has several thiol switches that may play a functional role by altering the conformation of KEAP1, impacting KEAP1 repression of NRF2 (Figure 2). Furthermore, NMDAR function itself is under direct redox regulation; extracellular domains on NMDAR subunits GluN1 and GluN2A contain thiol groups, that when oxidized reduce the likelihood and duration of NMDAR channel opening (78). Intracellular redox state also impacts NMDAR function, with shifts towards oxidation resulting in hypofunction (79) (Figure 2).

Indeed, there is a tight interaction between NMDAR function and redox status. Synaptic NMDAR activation boosts NRF2/ARE gene transcription including the transcription of glutamate-cysteine ligase, thus increasing glutathione synthesis (80). NMDAR blockade by ketamine in mice disrupts excitatory/inhibitory (E/I) balance in cortical circuits, affecting parvalbumin interneurons through enzymatically-induced NADPH oxidase (NOX-2) ROS generation (81). Reduced NMDAR activity thus lowers antioxidant defenses. In addition, serine racemase activity is inhibited by oxidation of its redox-sensitive thiols (82), reducing availability of the NMDAR co-agonist d-serine. Notably, NMDAR hypofunction (83), parvalbumin interneuron impairments (84, 85), and reduced gamma oscillations (84, 85) were all observed in a glutathione-deficit mouse model (*Gclm* KO).

Evidence of Redox Dysregulation in Schizophrenia

The symptoms and neuropathology of schizophrenia emerge and progress in a trajectory that can be roughly divided into three phases: *prodromal*, transitioning with a first episode to *early* (a 1–5 year period), and then to *chronic*. Regarding the prodrome, research criteria based mainly on the presence of attenuated psychosis-like symptoms define a clinical high-risk syndrome; adolescents and young adults with the syndrome have an approximate 20% risk of developing a full-blown psychotic disorder within 2 years, and up to 30–35% with longer follow-up periods (86, 87).

Schizophrenia is characterized by decreased levels of redox substrates, especially glutathione. Schizophrenia proton MRS studies reported glutathione reductions in brain regions implicated in schizophrenia, including the anterior cingulate cortex, medial prefrontal cortex, striatum and thalamus (88–92). However, glutathione reductions were not found in other brain regions implicated in schizophrenia, including prefrontal regions (dorsolateral medial prefrontal cortex, orbital frontal cortex), the insula and visual cortex (90, 92). Schizophrenia studies using high-strength (7T) magnets reported reductions of glutamate, glutamine, and GABA in medial prefrontal regions including the anterior cingulate (90, 92) that were correlated with glutathione levels (92), suggesting a link between redox dysregulation and interneuron dysfunction. Glutathione may be a reservoir for glutamate, thus the reductions in glutamate could also be due to reduced glutathione cycling (93). In contrast, one group reported glutathione elevations in the medial temporal

lobe in subjects with early phase schizophrenia, however whether brain glutathione levels could be specifically quantified with the described method is unclear [reviewed in (94)]. Postmortem studies found glutathione reductions in prefrontal cortex and striatum (95, 96). Using ^{31}P-MRS, investigators found lower ratios of NAD+/NADH in medial prefrontal cortices of schizophrenia relative to comparison subjects, further indicating redox dysregulation towards a pro-oxidant state (97). Erythrocyte ratio of glutathione peroxidase to reductase as well as glutathione peroxidase activities were negatively correlated with medial prefrontal cortical glutathione in male early phase schizophrenia patients, in contrast to controls where the correlation was positive (98). This finding suggests failure of shifting the glutathione system towards production of reduced glutathione in schizophrenia. Furthermore, erythrocyte glutathione levels were lower in psychosis converters versus nonconverters, with an area under the receiver operating curve of 0.82 (4). Studies of redox substrates and enzymes from body fluids have yielded mixed results, possibly related to *ex-vivo* alterations that often occur unless preventative measures are taken during biospecimen collection, processing, and storage (see Supplement for details).

Experimental medicine studies targeting brain glutathione levels lend support for a causal relationship between redox dysregulation and schizophrenia etiopathology. Supplementation with N-acetyl-cysteine (NAC), a bioavailable form of the rate-limiting amino acid for glutathione synthesis, led to increased brain cysteine and glutathione levels in conditions associated with oxidative stress; NAC supplementation in the absence of oxidative stress had little effect (99–102). Moreover, findings from various human conditions and rodent models suggest that brain glutathione levels drop with oxidative stress only when the glutathione system is overwhelmed and cysteine pools are depleted. Under those conditions brain glutathione levels normalize when cysteine is provided. However, under physiologic conditions redox control mechanisms function to maintain glutathione levels appropriate for cellular demands, thus reducing effects of supplemental NAC.

Nonetheless, a placebo-controlled trial found oral NAC supplementation increased medial prefrontal glutathione levels in early phase schizophrenia (103). Other placebo-controlled trials found that NAC improved scores for positive symptoms, negative symptoms, and cognition (103–109). In early phase schizophrenia NAC improved functional connectivity between the anterior cingulate cortex and isthmus (110), as well as integrity of white matter in the fornix, in correlation with brain glutathione level increases (111). This correlation links glutathione redox dysregulation to white matter impairments in schizophrenia. Furthermore, in two NAC trials ERP biomarkers of NMDAR function (N50/100 and mismatch negativity) improved with NAC (104, 112). linking redox dysregulation to the NMDAR hypofunction hypothesis, albeit to somatostatin rather than parvalbumin interneuron dysfunction.

Oxidative damage is evident in peripheral blood of persons with schizophrenia. Levels of oxidatively damaged proteins and oxidatively-damaged lipids have been reported in both first episode and chronic schizophrenia (73). Furthermore, in a cohort of 71 clinical high-risk and 35 unaffected subjects, baseline levels of oxidatively damaged lipids (MDA-LDL) were significantly higher in subjects that converted to psychosis compared to nonconverters and unaffected subjects (3). In 113 clinical high-risk subjects enrolled in an omega-3 clinical

trial, 92% of the high-risk subjects had baseline levels of oxidatively damaged lipids above the range of expected levels in healthy individuals (113).

A genetic polymorphism reducing the efficiency of glutamate-cysteine ligase (the enzyme for the rate-limiting step in glutathione synthesis) (114) was associated with lower blood glutathione levels in both early schizophrenia and control subjects (114, 115). Furthermore, medial prefrontal cortical glutamate levels were lower in schizophrenia relative to unaffected subjects (p=0.01), glutathione levels positively correlated with glutamate levels only in subjects with the low-risk genotype (98). Subjects with the high-risk genotype had lower medial prefrontal cortical glutathione levels, independent of disease status. In addition, white matter integrity along the cingulum bundle was significantly correlated with medial prefrontal glutathione in both patients and comparison subjects (72). These findings suggest that in humans reduced capacity to synthesize glutathione increases schizophrenia vulnerability, however emergence of schizophrenia may require additional risk factors especially during critical developmental windows [reviewed in (75)].

Rodent Models Link Redox Dysregulation to Human Neuropathological Findings

Human studies may suggest pathological mechanisms but are limited in their capacity to verify mechanisms at the molecular level. Various rodent models involving genetic and/or environmental manipulations linked to psychosis risk in humans partly bridge this gap. Examples include: inducing NMDAR hypofunction using ketamine/PCP/MK801 administration; targeting genes identified from large schizophrenia genome-wide association studies (116) such as *Grin2a* (coding for the non-obligatory GluN2A NMDAR subunit involved in adolescent brain maturation) knock-out (KO) or serine racemase (critical to synthesis of d-serine, a NMDAR co-agonist) KO; inflicting neurodevelopmental insults/lesions (e.g. MIA, MAM, NVHL); and interrogating genetic syndromes with elevated psychosis risk such as 22.q.11 deletion [reviewed in (6)]. Shared features of these models include behavioral, cognitive, electrophysiological, and cellular disturbances, with degrees of homology to schizophrenia.

Common molecular features of numerous rodent models involving schizophrenia risk factors include reduced numbers of parvalbumin interneurons and perineuronal net alterations linked to disruption of redox homeostasis (5, 6). For example, the serine racemase KO mouse was characterized by a 26% reduction of parvalbumin interneuron numbers, a 35% reduction of numbers of parvalbumin interneuron with perineuronal nets, and a 410% increase in DNA oxidative damage (6). Furthermore, parvalbumin interneuron/perineuronal net reductions were correlated with DNA oxidative damage. The *Grin2a* KO mouse had delayed maturation of parvalbumin interneurons and their perineuronal nets in the anterior cingulate cortex (117). In addition, the expression of genes involved in glutathione and related thioredoxin/peroxiredoxin systems were lower, suggesting a vulnerability to redox dysregulation and oxidative stress. When subjected to a “second-hit” known to increase oxidative stress [administration of a dopamine reuptake inhibitor as ROS are a by-products of dopamine metabolism and autooxidation (118, 119)] during early adolescence *Grin2a* KO

mice developed multiple abnormalities by adulthood. These included DNA oxidative damage, microglia activation, reductions in numbers of parvalbumin interneurons and parvalbumin interneurons with perineuronal nets and reduced high frequency (gamma) oscillatory power (117). Interestingly, a conditional *Grin2a* KO mouse model demonstrated that GluN2A NMDAR subunits on parvalbumin interneurons are required for ketamine-induced increase in gamma oscillatory power (120). The administration of NAC ameliorated *Grin2a* KO mouse model pathology (117, 121, 122), consistent with the effects of NAC in other models: ketamine (123); MK-801 (121, 124); neonatal ventral hippocampal lesion (NVHL) (122, 125), perinatal infection/peripubertal unpredictable stress (126) and maternal immune activation (MIA) (127).

Consistent with involvement of redox dysregulation in the etiopathology of schizophrenia, drug and genetic manipulations producing redox imbalance in rodents induced homologies of behavior, cognition, and cellular disturbances characteristic of schizophrenia [reviewed in (6)]. Reductions in glutathione alone caused increased excitability of CA1 pyramidal neurons in the hippocampus and NMDAR hypofunction (reduced excitatory postsynaptic receptor response related to increased oxidation at the NMDAR redox site) (83). In addition, glutathione reduction impaired NMDAR-dependent long-term potentiation (83, 128). Rodents subjected to glutathione reduction paired with administration of a dopamine reuptake inhibitor (a “second-hit” elevating ROS) exhibited reduced numbers of parvalbumin interneurons in the anterior cingulate but not somatosensory cortices (129).

A transgenic mouse model of redox dysregulation, the glutamate-cysteine-ligase modulatory subunit knock-out (*Gclm* KO), has a 70% reduction in brain glutathione levels (130) and behavioral homologies to schizophrenia (131, 132). In *Gclm* KO mice, parvalbumin interneurons and perineuronal net deficits emerged in a spatio-temporal sequence that paralleled regional brain maturation, appearing first in thalamic reticular nuclei, followed by the amygdala and lateral globus pallidus, then the ventral hippocampus, and lastly anterior cingulate cortex (133). Parvalbumin interneuron/perineuronal net deficits were highly correlated with oxidative DNA damage in these brain regions throughout development. The dorsal hippocampus was unaffected, despite reductions in glutathione similar to those of the ventral hippocampus (85). A possible explanation for this regional vulnerability to oxidative stress relates to the richer dopaminergic innervation of the ventral compared to the dorsal hippocampus (134, 135) and thus higher ROS load (118, 119). Interestingly, Grace and collaborators (136) demonstrated in the MAM model that elevated dopamine neurotransmission in the mesolimbic system resulted from parvalbumin interneuron impairments in the ventral hippocampus, as increased ventral hippocampal activity caused the nucleus accumbens to strongly inhibit the ventral pallidum, that in turn increased the number of spontaneously active ventral tegmental area dopamine neurons (137).

This could be at the basis of elevated presynaptic dopamine release in the striatum of clinical high-risk subjects who converted to psychosis (12, 13). Similar to findings in the *Gclm* KO mice, a post-mortem schizophrenia study found reductions of parvalbumin interneurons/perineuronal nets in thalamic reticular nuclei (138). Thalamocortical circuits involving thalamic reticular nuclei have been implicated in the generation of mismatch negativity (51),

suggesting a link between redox dysregulation impacting thalamic reticular parvalbumin interneurons and impaired generation of mismatch negativity in schizophrenia.

As with the *Grin2A* KO mouse (84), in the *Gclm* KO developmental reductions in parvalbumin interneurons/perineuronal nets in the cingulate cortex normalized in adulthood, indicating maturational delay (117, 135). However a “second-hit” involving experimentally-induced increases in ROS (via elevated dopamine) during adolescence resulted in reductions of parvalbumin interneurons/perineuronal nets by adulthood, effects that were rescued by NAC (135). In addition, proliferation and maturation of oligodendrocyte precursors were impaired in the anterior cingulate cortex of *Gclm* KO mice, an effect that was reversed with the administration of NAC (74).

A mechanism connecting parvalbumin interneuron redox dysregulation to microglia activation and perineuronal net reductions was identified in the *Gclm* KO mouse (135) (Figure 2). This mechanism involved activation of the protease MMP9 by oxidation of its redox modulatory site (139), an effect that peaked around puberty and declined by adulthood. Receptor for advanced glycosylation end-product (RAGE) has an intracellular and an extracellular domain. Activated MMP9 induced shedding of the extracellular and translocation of intracellular RAGE to the nucleus. Activation of the transcription factor NFKB occurred, possibly driven by intracellular RAGE nuclear translocation, leading to synthesis and secretion of cytokines including IL1B, IL6, TNFα to the extracellular compartment. These cytokines then induced microglia activation and microglial ROS production, perpetuating the oxidative stress process. Indeed, activated microglia release ROS and MMP9 (135, 140) that both degrade perineuronal nets. The observed perineuronal net deficits were associated with both increases in extracellular MMP9 and microglia activation (135). Blocking MMP9 activity at early developmental stages prevented the oxidative-stress induced parvalbumin interneuron/perineuronal net deficits and microglia activation in adulthood, indicating that redox-mediated activation of MMP9 was causal to the feedforward potentiation loop between oxidative stress and neuroinflammation (135). While not examined in that study, microglia activation increases microglial pruning of synaptic spines (139) and perineuronal nets protect synaptic spines from degradation (37). Finally, in a reverse-translational application, early course schizophrenia subjects with high-risk glutamate-cysteine ligase genotypes had negative correlation of blood levels of RAGE with medial prefrontal cortical GABA and GABA/glutamate ratio; no such correlations were found in low-risk genotype and unaffected subjects (135). This suggests that RAGE elevation in blood might indicate early psychosis subjects with redox dysregulation impacting parvalbumin interneurons and/or excitatory/inhibitory imbalance.

Summary and Future Directions

Numerous rodent models involving genetic or environmental manipulations linked to psychosis risk in humans converge on redox dysregulation as a pathological mechanism affecting the anterior cingulate cortex, thalamus, ventral hippocampus, and amygdala; these regions have ample dossiers in human schizophrenia. Neuropathological consequences of redox dysregulation are not evident until adolescence and young adulthood, consistent with the timing of emergent pathology in human schizophrenia studies. Loss of parvalbumin

interneurons, perineuronal nets, neuropil, microglial activation and white matter deficits resulting from redox dysregulation are consistent with many of the neuropathological and psychopathology features found in schizophrenia. Supporting a causal role, oxidative stress is present during the prodromal stage and predicts subsequent psychosis. During the initial and chronic stages of schizophrenia antipsychotics may improve psychosis but have little impact on negative or cognitive symptoms that drive functional impairments. In contrast, NAC modestly improved negative symptoms and cognitive impairments in several schizophrenia clinical trials, suggesting ongoing redox dysregulation may contribute to these symptoms. In various rodent models early intervention with NAC prevented the emergence of neuropathological consequences of redox dysregulation, implying that interventions targeting redox dysregulation may not only ameliorate symptoms once schizophrenia has developed, but actually prevent the emergence of schizophrenia.

In addition to schizophrenia, oxidative stress is a characteristic of aging, neurodegenerative disorders such as Alzheimer's dementia [reviewed in (141)], and neurodevelopmental disorders such as autism, anxiety, depression and bipolar disorders [reviewed in (142)]. The molecular mechanisms linking redox dysregulation to Alzheimer's neuropathology appears tied to amyloid plaque and neurofibrillary tangles accumulation [reviewed in (143)], distinguishing the role of redox dysregulation in Alzheimer's disease from that of schizophrenia. Mood disorders frequently co-occurred in the clinical high-risk syndrome, affecting about three-quarters of subjects [reviewed in (144)]. Thus, it will be important to determine how biomarkers of oxidative stress and redox dysregulation relate to the varied clinical outcomes of the clinical high-risk syndrome.

While human and rodent studies offer compelling evidence implicating redox dysregulation in the etiopathology of schizophrenia, schizophrenia is highly heterogeneous thus other mechanistic pathways are likely involved. For example, redox dysregulation primarily impacts parvalbumin interneurons but does not directly explain alterations in somatostatin interneuron expression and impairments in mismatch negativity observed in schizophrenia, although it is conceivable that somatostatin interneuron alterations are secondary to parvalbumin interneuron dysregulation (51). It remains to be determined whether biomarkers of redox dysregulation such as lipid peroxidation products, RAGE levels, ERP paradigms such as the gamma-evoked steady state response or brain glutathione levels identify a "redox dysregulation" subtype of schizophrenia. As demonstrated by rodent models, experimental medicine paradigms targeting redox systems are powerful tools to identify causal mechanisms that should be exploited in human studies. In addition to NAC, several compounds such as sulforaphane (naturally occurring in the seeds and sprouts of cruciferous plants) are known to activate NRF2/ARE pathways and may prove valuable in experimental medicine studies (145).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Financial Support:

This work was supported by the National Institute of Mental Health: (grant U01 MH082004 to D.O.P.) and by National Center of Competence in Research (NCCR) “SYNAPSY - The Synaptic Bases of Mental Diseases” from the Swiss National Science Foundation (n° 51AU40_125759 to KQD)

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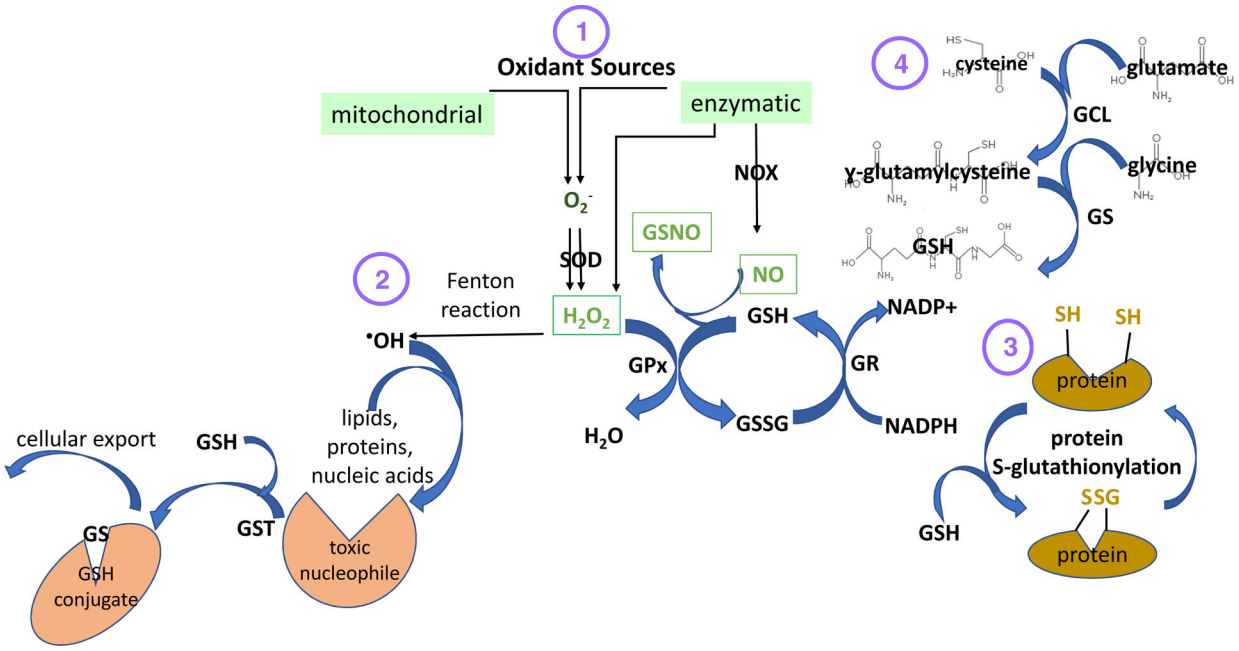

Figure 1. Central role of the glutathione system in regulating cellular redox state, protein activation, and oxidative damage.

(1) In animals, reactive oxygen species (ROS) are produced mostly by mitochondria but to a limited extend enzymatically. Superoxide is a reactive oxygen species generated by the mitochondrial electron transfer chain in the conversion of glucose and oxygen to ATP (the major energy currency in animals). Necessarily, cells are equipped with enzymatic antioxidant systems that efficiently neutralize ROS through controlled redox reactions. Reduction of mitochondrial-produced ROS begins with the conversion of superoxide to another oxidant, hydrogen peroxide, by superoxide dismutase enzymes with the highly reactive hydroxyl radical an intermediate. Three molecules with critical roles in cell signaling are generated enzymatically: hydrogen peroxide, nitric oxide, and S-nitrosoglutathione. Nitric oxide is produced by nitric oxide synthase. Nitric oxide combines with glutathione to produce S-nitrosoglutathione. Hydrogen peroxide is reduced by glutathione in a *reversible* reaction catalyzed by glutathione peroxidase, producing glutathione disulfide. Glutathione disulfide is reduced back to glutathione in a *reversible* reaction catalyzed by glutathione reductase, with NADPH serving as the electron donor. (2) Hydrogen peroxide may react with metals (the Fenton reaction) to form the highly reactive peroxide radical. The peroxide radical *irreversibly* oxidizes lipids, proteins, and nucleic acids, producing toxic nucleophiles. A second role of glutathione is to reduce toxic nucleophiles in a reaction catalyzed by glutathione transferase; the resulting glutathione:nucleophile conjugate is then exported from the cell, potentially depleting glutathione/cysteine stores. (3) A major focus of this paper is the critical role glutathione plays in controlling redox-mediated cell signaling (7). Thiol groups on proteins readily participate in *reversible* redox reactions that change the structure of the protein and hence its reactivity. Reversible redox reactions involving thiol groups is a ubiquitous strategy controlling numerous transcription factors, kinases, and phosphatases. One such reaction, protein S-glutathionylation, is shown here; others include the formation of disulfide bonds,

sulfenic acid, and S-nitrosoglutathione. (4) The rate-limiting step in glutathione synthesis is the combination of the amino acids cysteine and glutamate forming gamma-glutamylcysteine in a reaction catalyzed by glutamate-cysteine ligase. The availability of cysteine and glutatmate-cysteine ligase is rate-limiting in the synthesis of glutathione. The amino acid glycine is then added in a reaction catalyzed by glutathione synthase, to produce glutathione. Abbreviations: reactive oxygen species (ROS); superoxide (O^{-}_{2}); hydrogen peroxide (H_2O_2); peroxide radical ($^{\bullet}OH$); nitric oxide (NO); nitric oxide molecular oxygen (O_2); S-nitrosoglutathione (GSNO); thiol (SH);Superoxide dismutase (SOD); glutathione (GSH); glutathione disulfide (GSSGS); glutathione peroxidase (GPx); glutathione reductase (GR); glutathione-S-transferase (GST); glutamate-cysteine ligase (GCL); glutathione synthase (GS)

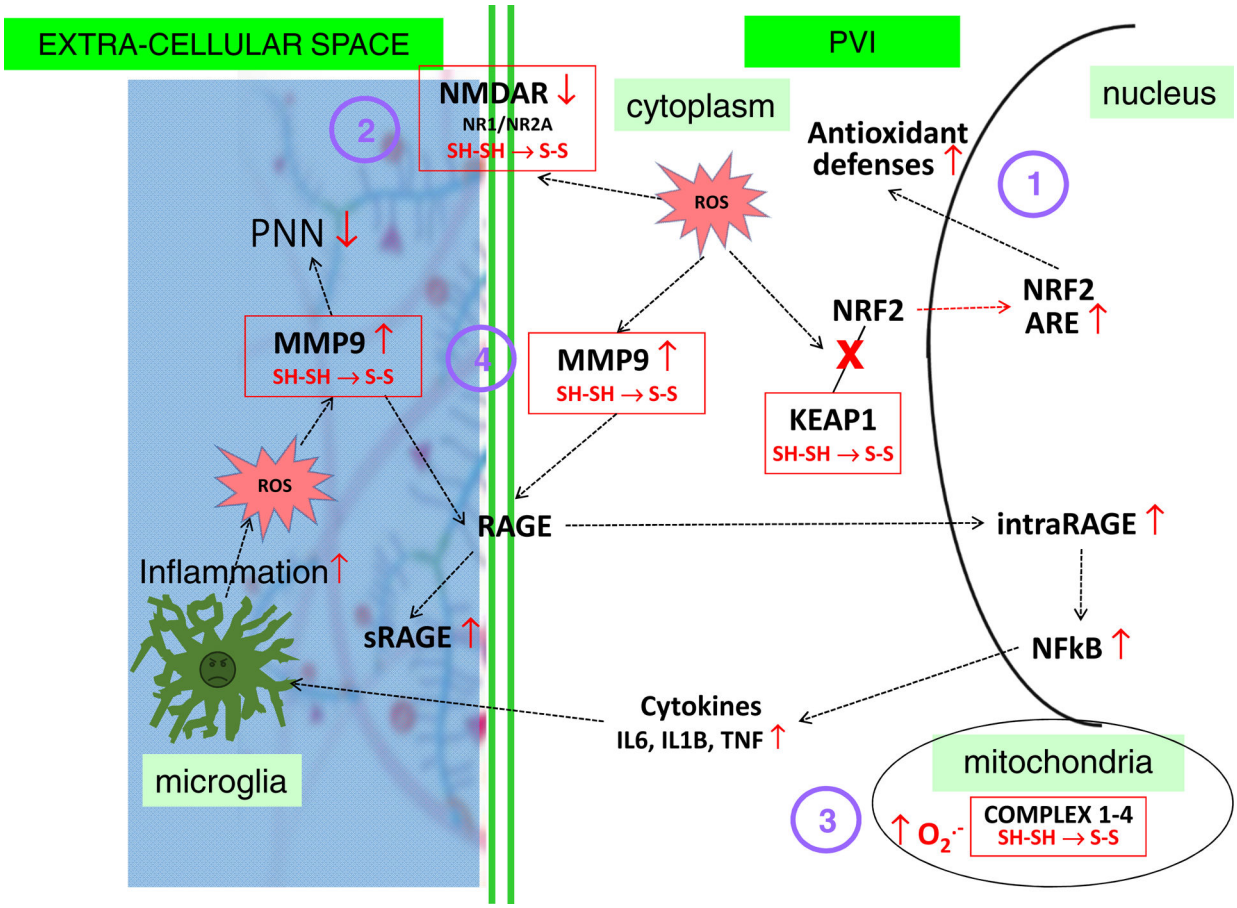

Figure 2. Redox regulation via oxidative stress sensitive targets in various cellular compartments:

Various redox sensitive targets are presented: the consequences of a redox imbalance leading to oxidation of the “redox-sensing” thiols, conformational and functional changes of target proteins are depicted in red. (1) The **Keap1-Nrf2** pathway is the major regulator of cytoprotective responses to endogenous and exogenous stresses caused by ROS and electrophiles (77). Through Nrf2 activation of ARE located at its promoter site, the transcription of glutamate-cysteine ligase is under the control of the Keap1-Nrf2 pathway. Under normal conditions Nrf2 is repressed by Keap1. Under oxidative stress, Nrf2 is derepressed and translocates to the nucleus where it binds to ARE and activates transcription of ARE-responsive genes, leading to enhanced glutathione synthesis through increased expression of glutathione-cysteine ligase (77). Interestingly, Keap1 is a very cysteine-rich protein and the thiol switches at C151, C273, and C288 (146) may play a functional role by altering its conformation. (2) There is a tight interaction between **NMDAR** (subunits NR1, NR2A) hypofunction and redox dysregulation: a) Activation of synaptic NMDAR boosts intrinsic antioxidant defenses, through direct transcriptional control of the glutathione system, promoting its synthesis, recycling, and utilization (80); NMDAR hypoactivity during development thus leads to deleterious loss of antioxidant control and increased oxidative stress; NMDAR blockade by ketamine in adults disrupts excitatory/inhibitory balance in cortical circuits, affecting parvalbumin interneurons through NADPH oxidase-

induced ROS generation (81). b) Vice-versa, NMDAR is a target of redox regulation through the NR1 and NR2A subunits which possess extracellular redox-sensitive sites (78) within the M3-S2 and S2-M4 linkers (C726 and C780 of the ligand binding domain) (147, 148). Deletion of NR1 subunit of NMDARs in parvalbumin interneurons leads to parvalbumin and another marker of parvalbumin interneurons, GAD67, expression deficits (149). (3) **Mitochondria**: Redox reactions are involved in regulating mitochondrial function via redox modification of specific redox sensing thiols in subunits of mitochondrial respiratory chain complexes. Oxidative thiol-modifications of specific cysteine thiols located in the 51 kDa- and 75 kDa-subunits of complex I result in a reduction of its catalytic activity (150). Emerging evidence points to the involvement of mitochondrial dysfunction with alteration of network morphology and activity of complex I in schizophrenia (64). (4) There is feedforward potentiation loop between oxidative stress and neuroinflammation involving the following steps: activation of MMP9 through its redox thiol switch by oxidative stress, leading to shedding of the extracellular domain of RAGE, sRAGE and the translocation of the intracellular domain of RAGE to the nucleus, followed by activation of the transcription factor Nfkb, secretion of pro-inflammatory cytokines, microglia activation, and further ROS production and oxidative stress during juvenile postnatal development. Blocking MMP9 activation prevented this sequence of alterations and rescued the normal maturation of parvalbumin interneurons/perineuronal nets, even if performed after an additional insult that exacerbated the long-term interneurons/perineuronal net impairments. MMP9 inhibition at early developmental stages prevented the interneurons/perineuronal nets deficit in adulthood (135). Abbreviations: Kelch-like ECH-associated protein (KEAP1); nuclear factor, erythroid 2 like 2 (NRF2); antioxidant response elements (ARE); reactive oxygen species (ROS); glutathione (GSH); glutamate-cysteine ligase (GCL); n-methyl-d-aspartate receptor (NMDAR); NMDA receptor subunit 1 isoform (NR1); NMDA receptor subunit 2a isoform (NR2A); (parvalbumin interneurons (PVI); oxidized thiols (S-S); reduced thiols (SH-SH); matrix metalloproteinase 9 (MMP9); receptor for advanced glycosylation end product (RAGE); extracellular soluble domain of RAGE (sRAGE); intracellular domain of RAGE (intraRAGE); nuclear factor NF-kappa-B (Nfkb); interleukin 6 (IL6); interleukin 1b (IL1b); tumor necrosis factor alpha (TNF); perineuronal nets (PNN)