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Review

Review

Redox and Immune Signaling in Schizophrenia: New Therapeutic Potential

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Abstract

Redox biology and immune signaling play major roles in the body, including in brain function. A rapidly growing literature also suggests that redox and immune abnormalities are implicated in neuropsychiatric conditions such as schizophrenia (SZ), bipolar disorder, autism, and epilepsy. In this article we review this literature, its implications for the pathophysiology of SZ, and the potential for development of novel treatment interventions targeting redox and immune signaling. Redox biology and immune signaling in the brain are complex and not fully understood; in addition, there are discrepancies in the literature, especially in patient-oriented studies. Nevertheless, it is clear that abnormalities arise in SZ from an interaction between genetic and environmental factors during sensitive periods of brain development, and these abnormalities disrupt local circuits and long-range connectivity. Interventions that correct these abnormalities may be effective in normalizing brain function in psychotic disorders, especially in early phases of illness.

Keywords: Oxidative stress, neuro-inflammation, parvalbumin neurons, schizophrenia, glutathione, NAD/NADH

INTRODUCTION

This review covers 2 rapidly growing and related aspects of biology that have major implications for brain function: redox and immune signaling. Evidence suggests that these intertwined processes play a role in neuropsychiatric conditions such as schizophrenia (SZ), bipolar disorder, autism, and epilepsy. We are at an exciting time in neuropsychiatry where pathophysiology of these conditions is becoming better understood, and our focus on redox and immune signaling can lead the way to development of novel treatment interventions.

The role of redox biology in the brain is yet not fully delineated, but we know that the dynamic balance between oxidative and reductive reactions in our cells is a critical process for all of biology and medicine. Likewise, neuroinflammation is a complex and dynamic process involving the innate and adaptive immune systems, and its role varies from physiology to pathology depending on stage of brain development. Impairments in these processes may arise from an interaction between genetic and environmental factors during sensitive periods of brain development. These alterations will affect brain maturation at both the local circuitry and long-range connectivity levels, contributing to the pathophysiology of psychiatric disorders.

We will present emerging attempts to capitalize on translational approaches favoring 2-way interactions between clinical and preclinical research with a special emphasis on SZ, where this literature is most developed. Indeed, thanks to animal and in vitro models, the redox and immune network can now be studied at various levels, from genetics to circuitry and cognitive and behavioral phenotyping. The use of state-of-the-art methodologies allows precise analysis of brain redox biology at the molecular, cellular (e.g., neurons, astrocytes, oligodendrocytes, microglia), and subcellular (e.g., membrane, cytosol, mitochondria, nucleus) levels as well as analysis of its dynamic evolution and spatio-temporal trajectory starting with early development. If such findings can be translated to patients, they may clarify mechanisms underlying abnormal structural and functional circuitry.

REDOX BIOLOGY IN PSYCHIATRY

General Background

Oxygen is essential for life, and yet, due to its strong electronegativity, this life-giving element can destabilize biomolecules by creating atomic radicals with unpaired electrons during oxidative

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phosphorylation. These reactive oxygen species (ROS) have the ability to damage lipids, proteins, and nucleic acids as well as alter posttranslational modifications (Pizzino et al., 2017). These phenomena are observed in traumatic tissue damage, cancer, and many other conditions (Jones and Sies, 2015). Due to these reasons, redox balance historically has been considered primarily in pathological contexts. On the other hand, emerging evidence now indicates that ROS may also play roles as signaling molecules in normal biological processes such as metabolic regulation and stress responses to support cellular adaptation to a changing environment (Sies and Jones, 2020). The terms "oxidative distress" and "oxidative eustress" have been proposed to capture the dual effects of ROS in the body (Sies et al., 2017).

Redox homeostasis is critical not only broadly in containing tissue damage over time but also in maintaining proper signaling in specific biochemical pathways. Multiple molecular systems are involved in these processes, including Nicotinamide adenine dinucleotide/Nicotinamide adenine dinucleotide phosphate (NADH/NADPH) and the thiol-disulfide molecule pairs (Cysteine/Cystine (Cys/CySS), glutathione [GSH]/GSSG, Thioredoxin/Peroxiredoxin/Sulfiredoxin (TRX/PRX/SRX)). In the brain, these molecular systems are well compartmentalized at the cellular and subcellular levels. In addition, spatiotemporal variation in production of redox-signaling molecules is exquisitely regulated by biological context (Go and Jones, 2013; Jones and Sies, 2015) and plays a role in critical processes such as the cell cycle and apoptosis signaling (Jones, 2010).

The balance between oxidative and reductive reactions in the body depends on multiple biochemical processes; primary among these is the electron transport chain (ETC), which produces ROS during oxidative phosphorylation. Redox sensor systems detect deviations from redox balance and trigger various compensatory responses, including upregulation of endogenous antioxidant molecules in the short term and reduced ETC activity and mitochondrial numbers in the long term (Iwamoto et al., 2005; Clay et al., 2011; Shadel and Horvath, 2015; Go et al., 2018). The principal molecule that maintains redox balance in the body, including in the brain, is GSH. GSH protects against oxidative damage in 3 ways: (1) serving as a cofactor for other "detoxifying enzymes" such as GSH peroxidase; (2) interconversion with its redox pair GSSG to generate water from hydrogen peroxide, thereby reducing ROS levels; and (3) helping regenerate other antioxidants such as vitamins C and E (Do et al., 2009). GSH levels are modulated by epigenetic regulation, a process itself impacted by ROS levels.

Redox Biology as Complex System

Redox reactions are positioned at the nexus of multiple critical biochemical pathways, including mitochondrial function/bioenergetics, immune signaling/neuroinflammation, and neuronal plasticity. Emerging evidence indicates that redox biology plays an important role in human brain function, and it is fitting to examine the evidence for redox abnormalities in disorders of the brain.

When considering pathological changes in a biochemical reaction network, it is important to consider the characteristics of such a complex system. Complex systems are resistant to perturbation and maintain large numbers of interdependent parameters within homeostatic ranges through countless feedback and compensatory mechanisms. This leads to 3 insights that are relevant to our discussion. First, it is insufficient and potentially misleading to study a single parameter and draw conclusions about the state of a complex system. One needs to understand the overall state of the system through the study of multiple parameters. Second, a complex system prioritizes homeostasis of important parameters within a normal range and may sacrifice parameters of lesser importance to accomplish this. Therefore, important parameters may be in a normal range in the pathological state of a complex system while less important ones become abnormal. Third, the trajectory of a complex system over time may contain more information than any cross-sectional snapshot. A relevant example from redox biology is the dynamic evolution of antioxidant enzyme activity and ROS-modified molecule levels (Lushchak and Storey, 2021). In a partially compensated situation, the enzyme activity is high while ROS-modified molecule levels are moderate; as oxidative stress (OxS) progresses, enzyme activity fails, but ROS-modified molecule levels rise higher (Figure 1, top panel). Many of these concepts are discussed in pathophysiology research under the rubric of network medicine (Chan and Loscalzo, 2012), although they have not been widely considered in psychiatry. The concept of network medicine also entails considering multiple biological processes together and not in isolation. This is relevant for understanding the relationships between redox biology and immune signaling, as we shall see.

Redox in SZ: A Translational Approach to Redox Profiling

Redox dysregulation represents 1 "hub" of convergence between genetic and environmental risk factors for SZ during neurodevelopment (Do et al., 2009). The genetic vulnerability factors involve either redox regulation genes directly affecting GSH metabolism (Gysin et al., 2007; Rodriguez-Santiago et al., 2010; Gravina et al., 2011) or genes indirectly related to OxS, including DISC1, PROD, G72, NRG, and DTNBP1. Environmental insults associated with psychiatric disorders, including perinatal insults and childhood trauma (Brown, 2011), generate ROS as well (Do et al., 2009).

The impact of redox dysregulation has been investigated on 2 types of cells: (1) fast spiking parvalbumin interneurons (PVI) in cortical (prefrontal, hippocampal) and subcortical regions, for example, thalamus reticular nucleus (Behrens et al., 2007; Steullet et al., 2018), amygdala (Cabungcal et al., 2019) (Cabungcal et al., 2019), globus pallidus (Cabungcal et al., 2019); and (2) oligodendrocyte precursor cells. Both cell types are characterized by high oxidative metabolism and regulate neural network synchronization underlying cognitive, affective, and social functions.

Redox and Neuroimaging in Patients

Clinically oriented studies provide some indirect support for redox abnormalities in psychiatric disorders. For example, there is evidence for reduced insulin sensitivity in first-episode psychosis associated with impaired cognitive function (Chouinard et al., 2019), a finding that likely presages the emergence of metabolic syndrome seen in chronic patients. Although these systemic metabolic abnormalities are consistent with redox dysfunction, they cannot be interpreted narrowly in a redox context because there are many alternative explanations for them.

Studies using cerebrospinal fluid (CSF) bring us 1 step closer to brain function. The primary redox-related metabolite studied in CSF is GSH (see Davison et al., 2018 for a review). There is little literature reporting reduced GSH levels in the CSF in SZ, and this has been interpreted as evidence of a redox abnormality in the brain in this condition (Do et al., 2000; Grima et al., 2003). Other redox markers have not been studied in CSF.

Neuroimaging studies provide some of the most direct evidence of brain abnormalities in psychiatric disorders. Magnetic

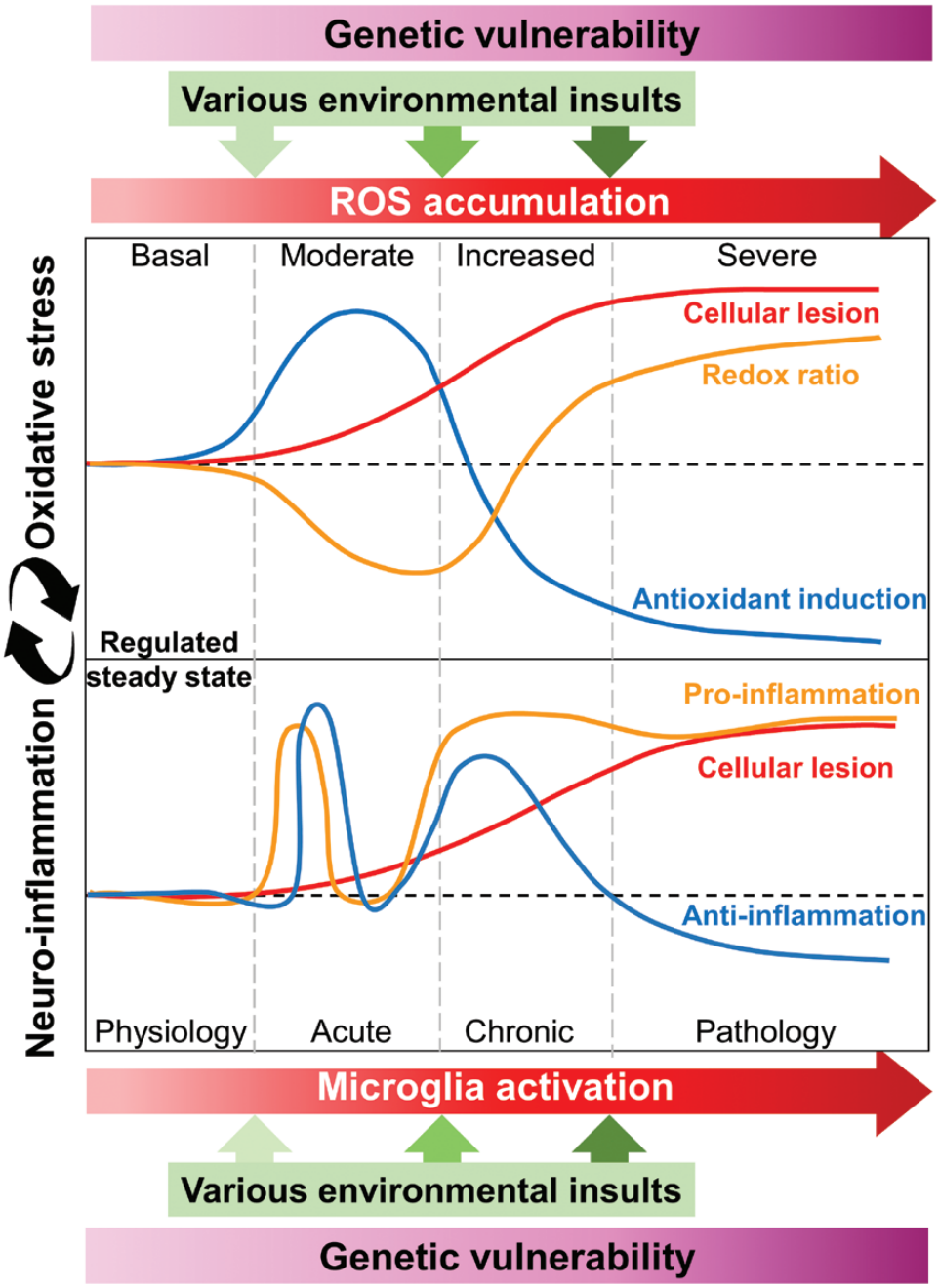

Figure 1. Schematic presentation of the dynamic, intensity-based evolution of redox regulation (upper panel) and its interaction with neuroinflammation (lower panel). In psychiatry, impairments of these critical processes arise from complex interactions between various genetic and environmental risk factors during sensitive periods of brain development. The evolution from basal physiologically regulated steady state to severe pathological state depends on the intensity of the induced oxidative stress (OxS) or microglia activation but also on an imbalance from the compensatory anti-antioxidant and anti-inflammatory systems. Upper panel: blue curve shows the path of an reactive oxygen species (ROS)-induced redox-sensitive parameter (e.g., the activity of an antioxidant enzyme). Red curve indicates the evolution of ROS-modified molecules (e.g., oxidized lipids, proteins, or nucleic acids). Yellow curve shows the path of the redox ratio (i.e., oxidized and reduced form of Nicotinamide adenine dinucleotide (NAD+/NADH)). Lower panel: the blue and yellow curves show the dynamic evolution of anti- and proinflammatory factors, respectively. Both are tightly regulated under physiological conditions but tip toward proinflammation in chronic and pathological sates; the red curve shows the evolution of brain cellular and molecular consequences of neuroinflammation.

resonance spectroscopy (MRS) studies specifically provide information on brain metabolites relevant for a variety of biochemical processes. In the redox biology domain, most attention has understandably fallen on GSH. This metabolite can be detected in vivo using proton (^{1}H) MRS. There are over a dozen published ^{1}H MRS studies measuring GSH in SZ patients using widely divergent technical approaches (scanner strength, pulse sequence, brain region, quantification approach, etc.). One meta-analysis published in 2019 (Das et al., 2019) reported an overall reduction in brain GSH in SZ, but not in bipolar disorder, with a small effect size ($d = 0.26$), suggesting a reduced antioxidant capacity in SZ. Of the 13 SZ studies included in that meta-analysis, however, only 2 reported a significant reduction in GSH. Two additional studies published since this meta-analysis have not found significant

reductions in brain GSH in SZ (Coughlin et al., 2021; Iwata et al., 2021). Heterogeneity in technical details and patient populations (e.g., genotype effects, Xin et al., 2016) can explain such a mixed picture, but the extant sizable literature suggests that it is unlikely that a major abnormality in GSH remains to be uncovered in SZ and that any reductions are very modest.

Cells can modulate their metabolic activity as a way to regain redox balance—for example, by slowing down oxidative phosphorylation when ROS exceed a certain level. Therefore, other metabolites relevant to metabolic processes and detectable using ^{1}H MRS may be of interest in understanding redox balance. Specifically, lactate is a glycolysis byproduct, and its accumulation as seen in SZ (Rowland et al., 2016) may indicate a relative shift away from oxidative phosphorylation to glycolysis. Changes in creatine (Ongur et al., 2009) and even the neurotransmitters glutamate and Gamma-Aminobutyric acid (GABA) may also be interpreted in similar contexts but do not provide direct insight into redox balance in SZ.

Another neuroimaging modality is phosphorus (^{31}P) MRS, which quantifies phosphorus-containing metabolites in the brain. Most relevant for redox biology is nicotinamide adenosine dinucleotide (NAD)-containing compounds NAD+ and NADH. These compounds differ by 1 electron and together comprise a "redox pair"; the NAD+/NADH ratio provides a direct measure of the redox potential of tissue. Two studies using ^{31}P MRS have reported abnormally low NAD+/NADH in SZ in 2 independent samples but collected by the same research group (Chouinard et al., 2017; Kim et al., 2017). The NAD+/NADH abnormality is quite pronounced (40%–50% below normal) and appears to be secondary to elevated NADH levels in the setting of normal NAD+. Interestingly, a lower NAD+/NADH ratio indicates reductive, not oxidative, stress while NADH accumulation is consistent with hyperglycemia in the setting of reduced oxidative phosphorylation rates.

Using similar logic as for ^{1}H MRS, we can examine other ^{31}P MRS measures for clues about redox balance. For example, there is evidence for reduced pH (indicating buildup of lactate) and for slowed ATP synthesis rates (indicating downregulated oxidative phosphorylation) in SZ using this modality (Du et al., 2014). These processes may reflect compensatory changes that reduce the production of ROS through oxidative metabolism and enhance glycolysis. These changes are also consistent with the observation of a reduced redox ratio.

These studies raise some interesting possibilities about the neurobiology of SZ, but we should note that they are often cross-sectional and have relatively small underpowered samples. Their conclusions can be strengthened by convergent evidence from other lines of research.

Redox Dysregulation and PVI Microcircuits

Cortical excitatory-inhibitory balance implemented through PVI GABAergic circuit activity is critical for high-frequency neuronal synchrony (Sohal et al., 2009) and physiological cognitive, emotional, and social behavior (Uhlhaas and Singer, 2010; McNally et al., 2013; for review, see Hu et al., 2014). The maturation of PVI and their associated perineuronal nets (PNN) defines a critical period of plasticity during postnatal development. PVI circuit alterations constitute a hallmark of SZ (Lewis et al., 2012; Mauney et al., 2013) and have also been reported in bipolar disorders (Kulak et al., 2013) and autism (Zikopoulos and Barbas, 2013). To support high-frequency discharge, fast-spiking PVI have elevated metabolic activity and oxidative phosphorylation (Harris et al., 2012) and are thus particularly vulnerable to redox dysregulation.

OxS in PVI (but not excitatory neurons) causes delay and prolongation of the critical period of cortical plasticity, that is, a failure to stabilize cortical circuits (Morishita et al., 2015). This may be attributable to a loss of ensheathing PNN networks of the extracellular matrix that act to limit plasticity (Hensch, 2005). Interestingly, PNN also play a role in protecting PVI against OxS (Cabungcal et al., 2013b). Thus, PNN may act as both a regulator of circuit activity as well as a defense system, with the caveat that excessive ROS can breach this defense with deleterious consequences.

As discussed above, GSH has been implicated in SZ pathophysiology; certain key GSH gene polymorphisms have functional consequences (Tosic et al., 2006; Gysin et al., 2007) that lead to low brain GSH in high-risk genotypes (Xin et al., 2016). In a genetic model (*Gclm*$^{-/-}$ mice), GSH synthesis is compromised (brain GSH levels diminished by 60%–70% throughout life; Duarte et al., 2012), preventing adequate redox balance regulation. These animals show a specific phenotype: in ventral but not in dorsal hippocampus, the mitochondrial DNA OxS marker 8-oxo-2'-deoxyguanosine is increased; this increase predates the emergence of PVI-immunoreactivity decreases, impairments of local neuronal synchronization in theβ/γ frequencies, and abnormalities in ventral hippocampus–related behaviors (Steullet et al., 2010). Furthermore, an inhibition of GSH synthesis restricted to PVI is sufficient to affect these interneurons (Morishita et al., 2015). Interestingly, additional insults at peripuberty but not in adulthood lead to severe impairments of PVI and PNN integrity that persist until adulthood in the prefrontal cortex in these animals (Cabungcal et al., 2013a). Administration of N-acetylcysteine (NAC), a precursor to GSH, prevents the morphological, biochemical, and physiological impairments when given during or after the insult (Dwir et al., 2021). This finding highlights childhood and peripuberty as critical periods of high brain vulnerability for environmental insults, analogous to the human case (Alameda et al., 2016). They also put in context the contribution of redox imbalance in a cohort of early psychosis patients (EPP) exposed to childhood trauma (sexual, physical, and emotional abuse) (Alameda et al., 2018). EPP with high peripheral oxidation status (GPX activity) had smaller hippocampal volumes and more severe symptoms, whereas those with lower oxidation status showed compensatory antioxidant regulation through the TRX/PRX systems and better cognition (Alameda et al., 2018). These observations indicate that genetic risk alone is generally compensated for and that additional environmental "hits" during development are required for the emergence of psychiatric symptoms. Depending on the intensity and duration of OxS produced, the adaptive response and its consequences could be quite different. With a modest and/or brief increase of ROS levels, homeostasis can be reestablished without lasting consequences. However, additional insults during sensitive developmental periods (such as peripuberty) may overwhelm compensatory mechanisms and lead to decreased antioxidant defenses and tissue damage.

Parallel observations have been made in several other animal models relevant to autism and SZ, ranging from genetic manipulations to environmental risk factors. These observations converge on OxS-induced PVI/PNN impairment as a "final common pathway" in the pathophysiology of SZ (Steullet et al., 2017). In these models there is a negative correlation between OxS markers and PVI/PNN integrity, suggesting that OxS may be at the origin of PVI/PNN deficit. Antioxidant defense systems are therefore potential therapeutic targets if redox regulators could be administered to vulnerable individuals early.

NAD/NADH Ratio and Bioenergetics: In Vivo Profiling in a Preclinical Model

The consequences of OxS are likely temporally and regionally specific during neurodevelopment (Cabungcal et al., 2019). In the *Gclm*$^{-/-}$ mice described above, ^{31}P MRS measurements in the prefrontal cortex show elevations in the NAD$^+$/NADH ratio from P20 to P90 and reductions at P250 (Skupienski et al., 2022). This pattern suggests a shift from OxS to reductive stress as animals mature from adolescence to adulthood. The reduction in adult *Gclm*$^{-/-}$ mice is also similar to that seen in adult patients with SZ (Kim et al., 2017). MRS studies in *Gclm*$^{-/-}$ animals also found changes in ATP, phosphocreatine, intracellular pH, glutamine and glutamate, and membrane phospholipid metabolites at P20 (Skupienski et al., 2020).

The preservation of PVI cells up to P90 may be partially attributable to NAD$^+$ upregulation, because NAD$^+$ plays important roles in brain energy production, DNA repair, and cellular signaling (Poljsak and Milisav, 2016). Thus, NAD+ may be a potential target for preventive treatment in high-risk populations. Investigation in other brain regions and the association with PVI deficits will guide the determination of a preventive time window of NAD$^+$-associated treatment in future studies.

Reciprocal Interactions Between Mitochondrial Dysfunction and Redox Dysregulation

PVIs have high mitochondrial content due to the energy demand required to sustain their fast-spiking characteristics. This renders them particularly susceptible to OxS and mitochondrial damage (Kann, 2016). Interestingly, in the *Gclm*$^{-/-}$ model with additional peripubertal insults, extranuclear localization of 8-oxo-2'-deoxyguanosine suggests mitochondrial DNA oxidation, potentially related to an accumulation of defective mitochondria. Khadimallah et al. (2022) also observed an upregulation of the microRNA miR-137 in brain PVI and blood, critically involved in mitophagy, in the same animal model. This finding suggests impaired mitophagy and accumulation of damaged mitochondria. The subunit COX6A2 of complex IV colocalized to PVIs and was also decreased. MitoQ, a mitochondria-targeted antioxidant, rescued these OxS-induced miR-137, COX6A2, mitophagy, and PVI alterations. Among 272 EPP, a subgroup also shows increased blood exosomal miR-137 and decreased COX6A2 as well as mitophagy markers compared with healthy controls, suggesting that parallel observations can be made centrally and peripherally in animal models and in blood samples from patients. The colocalization of COX6A2 and parvalbumin in exosomes of neuronal origin emphasizes that plasma exosomal COX6A2 levels reflect central PVI integrity. The EPP with abnormal miR-137 also showed a reduction of auditory steady-state response in gamma oscillations measured using EEG, worse psychopathological status and neurocognitive performance, and impaired global and social functioning. Because auditory steady-state response requires healthy PVI-related networks, alterations in miR-137/COX6A2 plasma exosome levels may represent a proxy marker of PVI cortical microcircuit impairment (Khadimallah et al., 2022). These results also suggest that impairment of PVI mitochondria lead to more severe disease profiles. This stratification allowed, with high selectivity and specificity (area under the curve=0.96), the selection of patients for treatments targeting brain mitochondria dysregulation.

NEUROIMMUNE, NEUROINFLAMMATION

Thus far we have focused on redox biology, reviewing patient, animal, and in vitro studies providing evidence for redox abnormalities in SZ. These studies are convincing, but they cannot be taken in isolation from other domains of biology, especially because redox biology is such a critical regulator of other processes. High on the list among these is immune signaling and neuroinflammation, critical brain processes tightly regulated by redox balance.

Neuroinflammation in Pathology and Physiology

The brain is access restricted from the rest of the body, with microglia as the primary immune cells that assure a rapid response to inflammatory stimuli. Moreover, a specific crosstalk between neurons and microglia allows microglial activation in inflammatory conditions and limits overactivation and inflammatory propagation (Prinz and Priller, 2014). The balance between proinflammatory and anti-inflammatory mediators is tightly regulated (Nakagawa and Chiba, 2014) to bring the system back to homeostasis. Interestingly, OxS is involved in signaling after an inflammatory challenge (Choi et al., 2012). This regulation is extremely important in the brain because an imbalance leads to chronic neuroinflammation through astrocytic activation, peripheral immune cell recruitment, neuronal injury, and blood–brain barrier disruption (Lucas et al., 2009). Activation of microglia induces their "priming," meaning that they are sensitized and will be more prone to react to future stimuli (Frank et al., 2012).

In addition to their role in pathological conditions, microglia and inflammatory mediators are involved in physiological processes both in the adult brain (Fontainhas et al., 2011) and during development. Of major interest is their role in synaptic pruning during the postnatal period (Paolicelli et al., 2011; Schafer and Stevens, 2015; Adelson et al., 2016). Therefore, microglial overactivation during development may lead to long-lasting anomalies in brain structural maturation.

The neuroinflammatory/immune process is highly dynamic, regulated so it responds to challenges but avoids tissue damage especially during brain development. The balance between proinflammatory and anti-inflammatory factors and the switch between acute and chronic neuroinflammatory states occurring at sensitive developmental stages may all contribute to the pathophysiology of SZ. Genetic and environmental factors may interact during brain development to generate a proinflammatory environment, prime the microglia, and lead to abnormal synaptic pruning and brain connectivity (Figure 1, bottom panel).

Immune Dysregulation/Neuroinflammation in SZ

There is broad support for a role of immune system dysregulation and neuroinflammation in SZ. At the adaptive immunity level, altered lymphocyte patterns with elevated CD3 and CD4 levels and CD4/CD8 ratios are found in drug-naïve first-episode patients (Miller et al., 2013). The neutrophil/lymphocyte ratio is also higher in chronically ill patients (Semiz et al., 2014). At the innate immunity level, peripheral blood mononuclear cells show increased Nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) activation in patients with first-episode psychosis (Song et al., 2009) as well as increased proinflammatory and decreased anti-inflammatory phenotypes (García-Bueno et al., 2014). Increased proinflammatory cytokines are seen at early stages of the disease and in nonmedicated patients (Upthegrove et al., 2014; Fond et al., 2018) as is anti-inflammatory cytokine dysregulation (Witte et al., 2014; Roomruangwong et al., 2020). Low-grade inflammation is associated with high risk for SZ, lower IQ, and impaired cognition (Kappelmann et al., 2019). Altogether, these data suggest an imbalance of the proinflammatory/anti-inflammatory peripheral phenotype of both the innate and adaptive immune systems, leading to a chronic inflammatory state in

at-risk states and EPP (Goldsmith et al., 2016). Indeed, increased proinflammatory cytokines were present in ultra-high risk individuals (Zeni-Graiff et al., 2016) and with the risk of conversion to psychosis (Perkins et al., 2015; Khoury and Nasrallah, 2018).

It is more challenging to interpret postmortem brain studies because these reflect the brain in a chronic schizophrenia state. Nevertheless, evidence for activated microglia and astrocytes as well as specific proinflammatory cytokines is commonly found in frontal regions and the hippocampus in such studies (Arion et al., 2007; Kesteren et al., 2017; Birnbaum et al., 2018). In vivo Positron emission tomography (PET) studies are now available, but these have been conflicting (Notter et al., 2018; Marques et al., 2019; McCluskey et al., 2020). In search for more reliable imaging technics for neuroinflammation, a diffusion weighted-MRI analysis of brain free-water was recently developed and found to be increased in EPP (Pasternak et al., 2016). The free-water increase is correlated with peripheral cytokine levels in patients (Biase et al., 2020), suggesting its role as a proxy for neuroinflammation. Despite the limitations of existing evidence, we can conclude that microglial activation appears to be more obvious during the early phase of psychosis, particularly during the prodromal phase.

These observations in patients are in line with a stage-dependent dysregulation in the balance between proinflammatory and anti-inflammatory phenotypes, suggesting a major role of inflammatory-related process in abnormal brain maturation at early disease phases.

Cause of Immune/Inflammatory System Dysregulation: Interaction Between Genetic and Environmental Risk Factors

Translational studies from animal models to patients and back delineate an interaction between genetic vulnerability toward abnormal inflammatory/immune response and environmental stressors occurring at a critical and sensitive period of brain development. Because microglia and various cytokines play a major physiological role during embryonic brain development and during childhood and adolescence, an environmental stimulus occurring during these periods may activate blood–brain barrier–mediated crosstalk along with either the peripheral or CNS immune system.

Genome-wide association study (GWAS) studies report that Major histocompatibility complex (MHC) loci have some of the strongest associations with SZ (Consortium, 2014). Other loci containing genes involved in the adaptive-immune system are also associated with SZ (Consortium, 2014; Marco et al., 2015). The MHC locus also contains the C4 gene, part of the complement system also found in synapses. The C4 protein tags synapses for elimination by microglia and is strongly associated with SZ (Sekar et al., 2016).

Maternal immune activation (MIA) appears to be an environmental risk factor associated with SZ. Large epidemiological studies show increased risk of developing illness in offspring of mothers who experienced infection during pregnancy, likely driven by the maternal immune system (Brown and Derkits, 2010). Increased maternal proinflammatory cytokines during gestation are associated with neurocognitive deficits (Rudolph et al., 2018) and aberrant functional connectivity (Rudolph et al., 2018). The maternal immune system can be activated by psychological stress, through the hypothalamic–pituitary–adrenal axis during pregnancy, with higher risks for SZ in the offspring (Khashan et al., 2008). Both glucocorticoids and cytokines impair brain development by altering neuronal precursor and oligodendrocyte maturation as well as microglia and astrocyte activation (Munhoz et al., 2006; Wohleb et al., 2011; Bilbo and Schwarz, 2012; Prinz and Priller, 2014). While maternal stress affects fetal brain development, psychosocial stress or adverse life events during early childhood also elevate risk for illness (Alameda et al., 2020) and increase serum Tumor necrosis factor alpha (TNFα) levels (Nicola et al., 2013). Abnormal activation of the hypothalamic–pituitary–adrenal axis during this developmental period increases inflammation and affects maturation of cognitive and emotional-related brain regions (Wohleb et al., 2011; Romeo, 2017). Moreover, the 2-hit model of MIA followed by subchronic unpredictable stress during puberty shows impairments in the GABAergic system (Giovanoli et al., 2014).

Consequences of Immune/Inflammatory System Dysregulation: Local Connectivity Impairments Leading to Clinical Symptoms

Many results point to the important role of microglia in synaptic pruning during the postnatal period (Stevens et al., 2007; Paolicelli et al., 2011; Schafer and Stevens, 2015). Therefore, inflammation leading to increased synapse elimination by over-activated microglia would be expected to affect PVI activity (Carlén et al., 2012). This excessive excitatory synaptic pruning may be involved in decreased PVI maturation during critical periods lasting into adulthood. This hypothesis is corroborated in MIA models showing decreased PVI and hypoconnectivity in PFC (Canetta et al., 2016) and increased synaptic pruning (Cieślik et al., 2020; Ikezu et al., 2021), leading to SZ-related behavior in adult offspring (Canetta et al., 2016).

The link between immune/inflammatory dysregulation and GABAergic impairments is also found in postmortem RNAseq analysis (Kim et al., 2016), with a reduction in inhibitory interneuron expression (Fillman et al., 2013), in association with high inflammation and poor verbal fluency (Fillman et al., 2016).

Proinflammatory cytokine levels are inversely correlated with cognitive performance (Johnsen et al., 2016; Fond et al., 2018) and positively correlated with symptom severity (Fernandes et al., 2016) in high-risk individuals, EPP, and chronic patients (Stojanovic et al., 2014; Zeni-Graiff et al., 2016). Increased C-reactive protein is also associated with reduced cortical thickness in cognitive-associated brain regions (North et al., 2021). Elevated cytokine levels may have consequences on brain morphology early in the disease, as suggested by a correlation between circulating proinflammatory cytokines and significant decline in frontal grey matter as well as a greater rate of expansion of the third ventricle in ultra-high risk converters (Cannon et al., 2015, Debost et al., 2016).

Interaction Between Immune/Inflammatory and Redox Systems: A Potential Drug Target

In this article, we have reviewed the evidence for abnormalities in redox and immune biology in the brain in SZ. These are critical and interlinked biological domains, but the interactions between them are complex and change over time. When processes in one domain begin to diverge from a healthy trajectory, this has an impact on the other. As depicted in Figure 1, the unfolding of spatiotemporally dynamic processes in a complex system is nonlinear and often unpredictable. Therefore, we suggest that these 2 domains be considered in relation to one another and not in isolation. We discuss this issue further below.

There is a reciprocal relationship between redox state and neuroinflammation: several inflammatory mediators are activated by ROS, and immune cells induce the secretion of ROS (Hsieh and

Yang, 2013). One promising substrate for this interaction is the receptor for advanced glycation end-product (RAGE) and the matrix metalloproteinase 9 (MMP9). Both molecules are activated by and mediate OxS and inflammation (Wautier et al., 2001; Devanarayanan and Nandeesha, 2015). MMP9 is involved in the modulation and degradation of the extracellular matrix, including the PNN (Pollock et al., 2014) and RAGE, and its ligands are elevated in the bloodstream of SZ patients (Steiner et al., 2009; Kouidrat et al., 2015). Interestingly, MMP9 protein was found to be increased and correlated with OxS markers in the serum of SZ patients (Devanarayanan and Nandeesha, 2015). In the *Gclm*$^{-/-}$ mice, RAGE shedding by MMP9 activation induces a feedforward loop, leading to NFkB activation, proinflammatory cytokine secretion, microglia activation, and further ROS production (Dwir et al., 2020). This vicious cycle between OxS and neuroinflammation emerges at an early developmental stage and leads to PVI/PNN maturation impairments, with long-lasting effects. Blocking MMP9-induced RAGE shedding, using a specific MMP9 at a specific developmental timepoint could rescue PVI maturation in adulthood. Interestingly, administration of NAC and an enriched environment rescues this deficit (Dwir et al., 2021), providing hope for translation of this therapeutic approach to patients. Increased soluble RAGE, reflecting RAGE shedding, and MMP9 activation are found in EPP. This increased RAGE was associated with decreased PFC GABA levels, in line with the preclinical findings (Dwir et al., 2020) Furthermore, RAGE levels are reduced by 6 months of NAC supplementation in EPP enrolled in an add-on, double-blind, placebo-controlled clinical trial (Conus et al., 2017; Dwir et al., 2021). This decrease was associated with increased PFC GABA and improvement of processing speed and working memory (Dwir et al., 2021), suggesting a causal role of MMP9/RAGE in the rescue of these cognitive impairments. Altogether, the MMP9/RAGE mechanism holds promise as a novel drug target for reducing the feedforward loop of OxS and inflammation and improving PVI maturation as well as cognitive symptoms at the earliest stages of psychosis.

DISCUSSION

An interesting pattern emerges when we consider the evidence for redox-related abnormalities in psychiatric disorders such as SZ. Data from animal models and metabolites measured in blood and CSF samples from patients all point to redox and immune abnormalities with elevated ROS and potential for cellular damage. OxS and inflammation impacts on the developing brain in general, and PVI in particular, are also consistent with existing theories on the pathophysiology of SZ. However, extensive neuroimaging research has failed to show a consistent in vivo abnormality in GSH, the primary antioxidant in the brain. The only direct measurements of the redox ratio in vivo have shown redox imbalance in the reductive stress direction, although those measurements were made at a single center and require replication (Du et al., 2014).

How can we interpret these observations? Taking the simplest case, it would in fact be astonishing if research showed lower GSH levels and an elevated redox ratio, with all indices pointing to OxS. Such a picture could emerge only in the absence of any compensatory changes, and this is unlikely in the brain. Instead, we can propose a dynamic scenario where inefficient oxidative phosphorylation (perhaps due to molecular lesions in Complex I of the ETC) (Ben-Shachar, 2017) leads to OxS during brain development. This situation has deleterious downstream impacts on PNN and various metabolites and perhaps depletes GSH as it is consumed to fight elevated ROS levels. Over time, this process might elicit a compensatory downregulation of oxidative phosphorylation to reduce ROS production and alleviate OxS. ROS production will then decline, GSH levels will return to normal, and NADH will accumulate because oxidative phosphorylation is no longer rapidly consuming NADH. These processes fluctuate back and forth, never reaching a true steady state but approximating a dynamic equilibrium that differs from the healthy condition.

We have outlined 1 potential scenario, but there are many others. There will surely be heterogeneity within the patient population and over time (i.e., early course vs chronic patients); GSH levels may be regulated with short time scales such that they briefly increase or decrease based on demand in ways that we cannot detect with MRI scans. We will be able to understand how the key mechanisms unfold when we are able to study the evolution of multiple parameters in this complex system over time. Translational approaches stimulating interaction between clinical and preclinical research hold great promise, because redox and immune networks can then be studied at various levels, from genetics to circuitry, to cognitive and behavioral phenotyping. To achieve this promise, we need to use state-of-the-art methodologies allowing precise analysis of brain redox and immune biology at the molecular, cellular, and subcellular levels as well as their dynamic evolution and spatio-temporal trajectories starting with early development. These methodologies can ideally be deployed first in in vitro and animal models and then translated to patients at various disease stages.

Potential Therapeutic Targets

We now turn our attention to the therapeutic potential of targeting brain redox and immune biology in SZ. Preclinical studies using animal models, as well as patient-derived blood and CSF studies, have identified some intriguing targets relevant to both processes (Perkins et al., 2015; Kim et al., 2019; Nakao et al., 2021; Cuenod et al., 2022). These include the GSH/GPX/Gred and TRX/PRX/SRX systems, the NAD/NADH system, the MMP9/RAGE pathway, and bioenergetics-related micro-RNAs. However, interpreting these results and translating them to the clinical setting is still challenging because of the myriad confounding factors in patient studies, such as metabolic syndrome, tobacco smoking, effects of medications used to treat the disorder, and so on. One important consideration in evaluating this literature is finding convergent evidence between animal models and clinical measures. For example, animal studies suggest that antioxidant treatments may not be useful in adults with SZ, although they may be useful during childhood and adolescence in at-risk individuals. Conversely, boosting ETC activity may not be useful in adolescents, but it may be in adults with SZ. As we develop deeper insights into the complex system of brain biochemistry in this condition, we may be able to better customize appropriate treatments.

Various molecules capable of impacting redox dysregulation/OxS have been tested in clinical trials, with mixed results (for review, see Cuenod et al., 2022): sulphoraphane acting through Nrf2 (Sedlak et al., 2018); the polyunsaturated fatty acids omega-3 (Amminger et al., 2020); D-serine, the glycine transporter inhibitor (Umbricht et al., 2014) or benzoate (Lane et al., 2013) modulating N-methyl-d-aspartate receptor (NMDAR) (Wu et al., 2021) activity; aspirin, minocycline, estrogens acting as anti-inflammatory agents (Cakici et al., 2019). One of the best-studied potential therapeutic compounds is NAC. In chronic SZ patients, a proof of concept, randomized, placebo-controlled add-on trial

with NAC revealed an improvement in negative symptoms (Berk et al., 2008) as well as mismatch negativity in EEG (Lavoie et al., 2008) and local synchronization. In EPP, a second proof-of-concept, randomized, placebo-controlled add-on trial showed that NAC increased brain GSH levels, thus suggesting a good target engagement. NAC also improved neurocognition, specifically processing speed (Conus et al., 2017), preattentional NMDAR-related mismatch negativity (Retsa et al., 2018), white matter integrity in the fornix (Klauser et al., 2018), and resting-state functional connectivity along the cingulum bundle (Mullier et al., 2019). In a subgroup of patients with high blood oxidative markers at baseline, NAC significantly improved positive symptoms in parallel with changes in peripheral redox status, thus paving the way for promising biomarker-guided treatment (Conus et al., 2017). The case of NAC also demonstrates the promise of personalized and mechanistically guided treatment development for future parallel efforts.

Furthermore, as the vicious cycle between OxS and neuroinflammation emerges at an early developmental stage, leading to long-lasting effects on PVI/PNN maturation, blocking MMP9-induced RAGE shedding using a specific MMP9 at peripuberty could rescue PVI maturation in adulthood. Future proof-of-concept clinical trials during adolescence with safe MMP9 inhibitors could thus be very promising. Given the safety profile of mitochondria-targeted antioxidants such as MitoQ, future stratified clinical trials based on bioenergetics biomarkers such as miR137 and COX6-A2 hold great promise for an early therapeutic approach (Khadimallah et al., 2022).

One other promising therapeutic direction for addressing these biochemical abnormalities is through NAD supplementation. We do not currently have direct means to modify the NAD+/NADH ratio, although this would be as important as supplementing total NAD levels. NAD-precursor molecules have not yet been tested in psychotic disorders, but several are orally bioavailable and cross the blood–brain barrier. Nicotinamide riboside is one such compound, and it is in development as a treatment for human diseases (Braidy and Liu, 2020; Reiten et al., 2021).

In summary, data discussed in this review highlight novel promising avenues of research into the pathophysiology of SZ: (1) the critical role of the spatio-temporal dynamics of redox regulation; (2) the importance of a tight interaction between neuroimmune processes and neuroinflammation on the one hand and redox dysregulation and OxS on the other; (3) the sensitive period around puberty, during which it may be possible to modulate the redox system and regulate excitatory-inhibitory imbalance and downstream dopamine hyperactivity (Sonnenschein and Grace, 2021); (4) a bidirectional translational approach using the same assessment endpoints in both animal models and well-phenotyped patients to provide insights about risk circuitry and mechanistic biomarkers; and (5) the development of proof-of-concept redox biomarker–guided clinical trials with MMP9 inhibitors, mitochondria-targeted antioxidants, and NAD precursors to pave the way for much needed precision diagnosis and early intervention for individuals with "clinical high risk" (Brady et al., 2023).

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Data availability

Further information and request for data and resources should be directed to and will be fulfilled by the Lead Contact, Kim Q Do (kimquang.docuenod@unil.ch).

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