Biomarkers in Early Psychosis

Evidence suggests that schizophrenia pathophysiology involve a dysregulation of antioxidant defenses, raising the question of its causal relationship with the disease phenotype. Using an animal model, the gclm−/− mice, deficient in glutathione (GSH) and thus prone to reactive oxygen species (ROS) excess, Kim Do’s group has demonstrated that, during development, redox dysregulation, leading to oxidative stress, can induce anomalies of the parvalbumine fast spiking interneurons (PVI) in hippocampus and anterior cingulate cortex, similar to that observed in patients brains. PVIs are indeed essential for local and distant synchronizations and cognitive functions. In gclm−/− mice, an additional stress during youth induces a prefrontal oxidative stress involving specifically PVIs deficits, an anomaly persisting into adulthood. In contrast, additional stress in adulthood has no effect on PVIs. The application of the antioxidant and GSH precursor N-acetyl-cysteine (NAC) throughout life prevents this deficit.

The perineuronal net (PNN), which enwraps PVIs and plays an important protective role against oxidative stress, is also permanently deficient in gclm−/− mice exposed to early stress. With Rossier we showed that PNN enwrapped PVIs express selectively Adamts8+15 and Mme, metalloproteases which degrade PNN. It is worth noting that PVIs integrity is necessary for the closing of critical periods of plasticity: With Hensch we showed that under conditions of PVI-specific redox dysregulation, critical period (as measured in V1) is prolonged concomitant with their loss of PNN.

Thus, if the redox homeostasis is deficient, insults during critical developmental periods induce permanent PVI impairments that can be prevented by redox modulators. In this context, it should be noted that Conus observed in schizophrenia patients an anamnestic difference between early trauma (associated with functional impairments and positive, negative, general symptoms) and late trauma (negative symptoms).

The following investigation emphasized two new aspects: first that another intervention, not involving the redox system, also lead to oxidative stress and PVI impairment; second that redox regulators can protect even when applied after the insults. In the well-established developmental “neonatal-ventral-hippocampal-lesion (NVHL)” schizophrenia model, which mimics the delayed emergence of phenotypes in adolescence, in
collaboration with Patricio O’Donnell, we observed that oxidative stress was induced during presymptomatic stages leading to prefrontal PVIs impairments. Juvenile treatment with NAC prevented the morphological (oxidative stress, PVIs), as well as electrophysiological and behavioral deficits relevant to schizophrenia. Adolescent treatment with NAC or the glutathione peroxidase mimic ebselen also reversed behavioral deficits. These findings suggest that presymptomatic oxidative stress yields abnormal adult brain function in a developmentally compromised brain, and highlight redox homeostasis as a potential target for early intervention. They also suggest that various factors can converge on oxidative stress.

**Deficits in NVHL rat model prevented by N-Acetyl-Cysteine**

![Graphs showing deficits in NVHL rat model prevented by NAC](image)

Cabungcal, Courtois, Do, O’Donell, Neuron, 2014

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In addition to the PVI vulnerability to oxidative stress, oligodendrocyte precursor cells (OPC) are also sensitive to redox status. This is of special interest as schizophrenia pathophysiology implies both abnormal redox control and structural dysconnectivity, related to myelin impairments. In a collaborative effort between clinical (P. Conus), imaging (P. Hagmann, R. Gruetter) and experimental (K. Do) groups, we investigated the interplay between glutathione and myelin. In control subjects, we observed, by multimodal brain imaging, a positive correlation between medial prefrontal GSH levels and both white matter integrity and resting-state functional connectivity along the cingulum bundle, suggesting a critical role of GSH in white matter integrity. In a translational approach, we showed in the prefrontal cortex of peripubertal gcml<sup>−/−</sup> mice, a decrease in mature oligodendrocyte numbers and in myelin markers. At the molecular levels, under GSH-deficit conditions, OPC showed a decreased proliferation and delayed maturation mediated by a dysregulation of Fyn kinase pathways. This was reversed by either NAC or Fyn kinase inhibitors. Interestingly, the regulation of Fyn mRNA and protein expression was also impaired in fibroblasts of patients deficient in glutathione synthesis. Thus, glutathione and redox homeostasis play a critical role in myelination processes and white matter maturation in the prefrontal cortex of rodent and human, a mechanism potentially disrupted in schizophrenia. 

**Glutathione deficit impairs white matter integrity: Fyn a potential molecular pathway**

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**Association between brain [GSH] and cingulum white matter integrity**

**Fyn kinase dysregulation in GSH deficient in oligodendrocytes**

**Fyn pathway**

**Increased Fyn mRNA in fibroblasts of GSH deficient early psychosis patients**

*Morin et al., Molecular Psychiatry 2015*
Further investigations are underway on other disease mechanisms, glutamate/NMDAR hypo-function and inflammation which also interact reciprocally with oxidative stress in a damaging feed forward process\(^9,10\).

**References**