
**SfN 2014—Redox Dysregulation in Schizophrenia**

January 13, 2015. On the morning of Monday, November 17, researchers from across many neuroscience disciplines gathered to hear a Neuroscience 2014 Presidential Special Lecture given by **Kim Do** of Lausanne University Hospital in Switzerland. Do discussed data suggesting that redox dysregulation interacts with glutamatergic dysfunction and neuroinflammation to produce both micro- and macrocircuit disturbances that ultimately lead to cognitive and affective symptoms of schizophrenia (Steullet et al., 2014).

The redox system is the collection of reactions—classified as either oxidations or reductions based on whether an oxygen molecule is gained or lost—that form the basis of biochemical processes. Too much oxidation leads to the accumulation of reactive oxygen species (ROS) that results in oxidative stress, a damaging cellular state implicated in many diseases. Do's group in Lausanne has been the most prominent in proposing this mechanism for the pathophysiology of schizophrenia. For example, they have reported that the antioxidant glutathione (GSH) is reduced in the cortex of subjects with schizophrenia, and several genes involved in GSH synthesis are associated with an increased risk for the illness (see also SRF related news report; SRF news report).

**Interneurons and oligodendrocytes affected**

Genetic deletion of the modifier subunit of glutamate-cysteine ligase (GCLM), a schizophrenia risk gene and the rate-limiting enzyme of GSH synthesis, produces a 60-70 percent decrease in GSH that Do and colleagues have used to model redox dysregulation (Steullet et al., 2010). GCLM knockouts show elevated levels of oxidative stress and, reminiscent of the illness, have lower numbers of PV immunoreactive neurons in the hippocampus accompanied by impaired ß/? oscillations, indicative of impaired neuronal synchronization. They also display impaired emotional, stress, and social behaviors, along with abnormal prepulse inhibition.

It appears that cortical microcircuits involving PV neurons are especially sensitive to a redox dysregulation, said Do. PV neurons are normally protected by the perineuronal nets that surround them, but Do showed that the developmental expression of perineuronal nets is delayed in GCLM knockouts (see SRF related news report; SRF news report). A reduction in perineuronal nets has also been reported in schizophrenia (see SRF related news report).

In addition to these PV interneuron changes resulting from genetically induced oxidative stress, Do and colleagues found that the addition of another stressor, when administered early in development but not during adulthood, exacerbates the oxidative stress (Cabungcal et al., 2013). When the researchers induced dopamine release in the GCLM knockouts, leading to the generation of ROS, the loss of PV neuron immunoreactivity was even more dramatic. The findings suggest that people at genetic risk for redox dysregulation are especially vulnerable to early-life environmental insults, said Do.

She then shifted gears to discuss the impact of redox dysregulation on long-range connections in schizophrenia. Do reviewed a large body of evidence pointing to deficits in oligodendrocytes, and the myelin they generate, in the illness. She also described a recent multimodal imaging study from her lab demonstrating that prefrontal GSH levels correlate with white matter integrity along the cingulum

bundle in subjects in the early phase of psychosis (Monin et al., 2014). Monin and colleagues also showed that GCLM mice exhibit impaired oligodendrocyte proliferation and maturation, as well as a reduced number of myelin markers.

Interestingly, N-acetylcysteine (NAC), an antioxidant and precursor of GSH, was able to restore both the PV interneuron and oligodendrocyte deficits in the animal model. For example, administration of NAC during pregnancy prevented the reduction in PV immunoreactivity as well as the compromised perineuronal nets in GCLM knockouts. These findings suggest that protecting against oxidative stress could be beneficial in schizophrenia, said Do. Indeed, add-on treatment with NAC has been shown to improve several types of symptoms, mismatch negativity, and electroencephalography (EEG) local synchronization in patients with schizophrenia, she added (see SRF related news report).

**Role of NMDA and neuroinflammation**

Glutamatergic and neuroinflammation abnormalities also seem to play a role in redox dysregulation of schizophrenia. The activation of NMDA receptors controls the GSH system, thereby boosting the antioxidant defense system, she said. In addition, NMDA hypofunction appears to generate oxidative stress and impair PV neurons (see SRF related news report). Do also reviewed a wide body of genetic, pathology, and clinical studies pointing to a role for neuroinflammation in schizophrenia (see SRF related news report; SRF news report). She then presented data showing that oxidative stress in peripubertal mice can lead to microglia activation.

In summary, a "hub" is formed by the redox, neuroimmune, and glutamatergic systems that, when altered during development, may disrupt the maturation of parvalbumin (PV) interneurons and oligodendrocytes, leading to several schizophrenia symptoms. The correction of redox dysregulation may be of therapeutic value.—Allison Marin.