Model of Schizophrenia Cortical Deficits Reversed With Antioxidants

August 6, 2014. In a new study published online August 6 in Neuron, an international collaboration offers up evidence linking the reported alterations in cortical interneurons in schizophrenia to oxidative stress.

Kim Do and colleagues at Lausanne University Hospital in Switzerland teamed up with Patricio O'Donnell's group at the University of Maryland in Baltimore to test the Lausanne group's long-standing hypothesis of oxidative stress in schizophrenia by using the neonatal ventral hippocampal lesion (NVHL) model that O'Donnell has employed to probe subtle miswiring of the prefrontal cortex.

The authors report evidence that NVHL produces oxidative stress in rat cortical interneurons, particularly those expressing parvalbumin, and that giving the animals an antioxidant throughout most of postnatal development, or even just in the last stages before adulthood, can reverse this finding, along with various deficits in neuronal chemistry and electrophysiology and brain function.

Linking up hypotheses

For many years, the two research groups have been working on separate hypotheses: O'Donnell's lab has investigated the delayed effects of neonatal hippocampal lesions in rats on the development of wiring in the prefrontal cortex. The researchers have proposed that the abnormalities that arise only in rat "adolescence" can model some aspects, particularly in the dopaminergic system, of schizophrenia pathophysiology (see SRF related news report and SRF related conference report). For their part, Do and Michel Cuenod have pursued evidence that the nervous system of people with schizophrenia is awash in reactive oxygen species that can harm neurons in various ways. In particular, they have focused on the possibility of a shortage of glutathione, which scavenges these oxidative molecules (reviewed in SRF related conference report).

In their joint study, co-first authors Jan-Harry Cabungcal, Danielle Counotte, Eastman Lewis, and their colleagues lesioned the ventral hippocampus in rat pups (postnatal days 7-9) and exposed them to the antioxidant N-acetyl cysteine (NAC) from P5 until P60, first through their mothers and later directly via drinking water.

Consistent with previous reports, the lesions resulted in changes to interneurons in prefrontal cortex (PFC), specifically to the expression of parvalbumin (PV) in NVHL rats versus sham-operated animals. NAC treatment reversed these changes, and in support of the idea that oxidative stress was a factor in the reduction in PV, the authors found significantly higher levels of the DNA oxidation marker 8-oxo-dG in cortical pyramidal cells and interneurons of the NVHL rats at P21.

The immunohistochemistry data were supported by electrophysiology in cortical slice and in-vivo preparations. Well-known abnormalities in PFC pyramidal cell synaptic function of NVHL mice were also corrected by the NAC treatment.

Finally, Cabungcal and colleagues zoomed out to look at information processing and sensorimotor gating, using mismatch negativity and prepulse inhibition (PPI) tests to probe for deficits that have

been found in people with schizophrenia. In both cases, NAC treatment normalized the alterations stemming from the neonatal lesions.

The authors also addressed one possible critique that the beneficial effects were due to effects on glutamate neurotransmission via the cysteine-glutamate transporter. However, both ebselen and apocynin antioxidants that do not affect glutamate levels rescued the PPI deficits in NVHL animals.

Questions for the future

"Our data suggest that oxidative stress in PFC is a core feature mediating alterations induced by the NVHL, and antioxidant treatment prevents these alterations," conclude the researchers.

How would the NVHL have produced oxidative stress? The authors speculate that the reduction in glutamatergic input during development places the PV-expressing interneurons in PFC under oxidative stress, citing evidence that NMDA receptor blockade can have this effect (see SRF related news report). However, they also note that this model of prefrontal dysfunction does not have to accurately reflect processes of schizophrenia in order to reproduce the pathophysiology of the disease.

The results are certainly intriguing, given that they present a possible therapeutic option that could be applied early in the disease, or even in the prodrome Cabungcal and colleagues were able to significantly improve prepulse inhibition by giving NAP beginning in rat adolescence (P35). The compound appears to have few major side effects, and it is currently used as a non-regulated supplement, though it would be hard to predict its effects on the developing nervous system. Hakon Heimer.

Reference:

Cabungcal JH, Counotte DS, Lewis EM, Tejeda HA, Piantadosi P, Pollock C, Calhoon GG, Sullivan EM, Presgraves E, Kil J, Hong LE, Cuenod M, Do KQ, O'Donnell P. Juvenile Antioxidant Treatment Prevents Adult Deficits in a Developmental Model of Schizophrenia. Neuron. 2014 Aug 12. Abstract