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Neuron Loss in Schizophrenia and Depression Could Be Prevented With an Antioxidant

Reports new study in Biological Psychiatry

Philadelphia, PA, March 13, 2013 – Gamma-aminobutyric acid (GABA) deficits have been implicated in schizophrenia and depression. In schizophrenia, deficits have been particularly well-described for a subtype of GABA neuron, the parvalbumin fast-spiking interneurons. The activity of these neurons is critical for proper cognitive and emotional functioning.

It now appears that parvalbumin neurons are particularly vulnerable to oxidative stress, a factor that may emerge commonly in development, particularly in the context of psychiatric disorders like schizophrenia or bipolar disorder, where compromised mitochondrial function plays a role. parvalbumin neurons may be protected from this effect by *N*-acetylcysteine, also known as Mucomyst, a medication commonly prescribed to protect the liver against the toxic effects of acetaminophen (Tylenol) overdose, reports a new study in the current issue of *Biological Psychiatry*.

Dr. Kim Do and collaborators, from the Center for Psychiatric Neurosciences of Lausanne University in Switzerland, have worked many years on the hypothesis that one of the causes of schizophrenia is related to vulnerability genes/factors leading to oxidative stress. These oxidative stresses can be due to infections, inflammations, traumas or psychosocial stress occurring during typical brain development, meaning that at-risk subjects are particularly exposed during childhood and adolescence, but not once they reach adulthood.

Their study was performed with mice deficient in glutathione, a molecule essential for cellular protection against oxidations, leaving their neurons more exposed to the deleterious effects of oxidative stress. Under those conditions, they found that the parvalbumin neurons were impaired in the brains of mice that were stressed when they were young. These impairments persisted through their life. Interestingly, the same stresses applied to adults had no effect on their parvalbumin neurons.

Most strikingly, mice treated with the antioxidant *N*-acetylcysteine, from before birth and onwards, were fully protected against these negative consequences on parvalbumin neurons.

“These data highlight the need to develop novel therapeutic approaches based on antioxidant compounds such as *N*-acetylcysteine, which could be used preventively in young at-risk subjects,” said Do. “To give an antioxidant from childhood on to carriers of a genetic vulnerability for schizophrenia could reduce the risk of emergence of the disease.”

“This study raises the possibility that GABA neuronal deficits in psychiatric disorder may be preventable using a drug, *N*-acetylcysteine, which is quite safe to administer to humans,” added Dr. John Krystal, Editor of *Biological Psychiatry*.

The article is “Early-Life Insults Impair Parvalbumin Interneurons via Oxidative Stress: Reversal by *N*-Acetylcysteine” by Jan-Harry Cabungcal, Pascal Steullet, Rudolf Kraftsik, Michel Cuenod, and Kim Q. Do (doi: 10.1016/j.biopsych.2012.09.020). The article appears in *Biological Psychiatry*, Volume 73, Issue 6 (March 15, 2013), published by Elsevier.

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Notes for Editors

Full text of the article is available to credentialed journalists upon request; contact Rhiannon Bugno at +1 214 648 0880 or Biol.Psych@utsouthwestern.edu. Journalists wishing to interview the authors may contact Kim Do at +41 21 643 65 65 or kim.do@chuv.ch.

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The journal publishes novel results of original research which represent an important new lead or significant impact on the field, particularly those addressing genetic and environmental risk factors, neural circuitry and neurochemistry, and important new therapeutic approaches. Reviews and commentaries that focus on topics of current research and interest are also encouraged.

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