MedicalXpress

Molecular link between diabetes and schizophrenia connects food and mood

June 8 2010

Defects in insulin function - which occur in diabetes and obesity - could directly contribute to psychiatric disorders like schizophrenia.

Vanderbilt University Medical Center investigators have discovered a molecular link between impaired insulin signaling in the brain and schizophrenia-like behaviors in mice. The findings, reported June 8 in *PLoS Biology*, offer a new perspective on the psychiatric and cognitive disorders that affect patients with diabetes and suggest new strategies for treating these conditions.

"We know that people with diabetes have an increased incidence of mood and other psychiatric disorders," said endocrinologist Kevin Niswender, M.D., Ph.D. "And we think that those co-morbidities might explain why some patients have trouble taking care of their diabetes."

"Something goes wrong in the brain because insulin isn't signaling the way that it normally does," said neurobiologist Aurelio Galli, Ph.D.

Galli's group was among the first to show that insulin - the hormone that governs glucose metabolism in the body - also regulates the brain's supply of dopamine - a neurotransmitter with roles in motor activity, attention and reward. Disrupted dopamine signaling has been implicated in brain disorders including depression, Parkinson's disease, schizophrenia and attention-deficit hyperactivity disorder.

Now, Galli, Niswender, and colleagues have pieced together the

molecular pathway between perturbed insulin signaling in the brain and dopamine dysfunction leading to schizophrenia-like behaviors.

The researchers developed mice with an insulin-signaling defect only in neurons (they impaired the function of the protein Akt, which transmits insulin's signal inside cells). They found that the mice have behavioral abnormalities similar to those frequently seen in patients with schizophrenia.

They also showed how defects in insulin signaling disrupt neurotransmitter levels in the brain - the mice have reduced dopamine and elevated norepinephrine in the prefrontal cortex, an important area for cognitive processes. These changes resulted from elevated levels of the transporter protein (NET) that removes norepinephrine and dopamine from the synaptic space between neurons.

"We believe the excess NET is sucking away all of the dopamine and converting it to norepinephrine, creating this situation of hypodopaminergia (low levels of dopamine) in the cortex," Galli explained. Low dopamine function in the cortex is thought to contribute to the cognitive deficits and negative symptoms - depression, social withdrawal - associated with schizophrenia.

By treating the mice with NET inhibitors (drugs that block NET activity), the investigators were able to restore normal cortical dopamine levels and behaviors. Clinical trials of NET inhibitors in patients with schizophrenia are already under way, Galli said, and these new data provide mechanistic support for this approach.

The findings also provide a molecular basis for interpreting previous reports of Akt deficiencies in patients with schizophrenia, as revealed by post-mortem, imaging and genetic association studies.

Galli and Niswender suggest that the insulin to Akt signaling pathway is critical for "fine-tuning" the function of monoamine neurotransmitters - dopamine, norepinephrine and serotonin - and that it can be impaired in many different ways.

"Dysregulation of this pathway - because of type 1 diabetes, because of a high-fat diet, because of drugs of abuse, because of genetic variations - may put a person on the road to neuropsychiatric disorders," Galli said.

Understanding the molecular link between insulin action and dopamine balance - the connection between food and mood - offers the potential for novel therapeutic approaches, the researchers said. The mouse model described in the current studies may be useful for testing schizophrenia and cognition-enhancing treatments.

More information: Siuta MA, Robertson SD, Kocalis H, Saunders C, Gresch PJ, et al. (2010) Dysregulation of the Norepinephrine Transporter Sustains Cortical Hypodopaminergia and Schizophrenia-Like Behaviors in Neuronal Rictor Null Mice. PLoS Biol 8(6): e1000393. doi:10.1371/journal.pbio.1000393

Provided by Vanderbilt University Medical Center