Insulin's brain impact links drugs and diabetes

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Insulin, long known as an important regulator of blood glucose levels, now has a newly appreciated role in the brain.

Vanderbilt University Medical Center researchers, working with colleagues in Texas, have found that insulin levels affect the brain's dopamine systems, which are involved in drug addiction and many neuropsychiatric conditions.

In addition to suggesting potential new targets for treating drug abuse, the findings raise questions as to whether improper control of insulin levels – as in diabetes – may impact risk for attention deficit hyperactivity disorder (ADHD) or influence the effectiveness of current ADHD medications.

The study, led by Aurelio Galli, Ph.D., in the Center for Molecular Neuroscience and Calum Avison, Ph.D., in the Institute of Imaging Science (VUIIS), appears online this week in the Public Library of Science Biology (PLoS Biology).

The psychostimulant drugs amphetamine and cocaine, as well as related medications for ADHD, block the reuptake of the neurotransmitter dopamine by dopamine transporters (DATs) and increase the level of dopamine signaling. Some of these compounds, including amphetamine, also cause a massive outpouring of dopamine through DATs.

The resulting surge of synaptic dopamine alters attention, increases

motor activity and plays an important role in the addictive properties of psychostimulants.

But the link between insulin status and dopaminergic function is not readily apparent.

“In the 1970s, there were articles showing that, in animals with type 1 diabetes, psychostimulants like amphetamine would not increase locomotor behavior,” said Galli, associate professor of Molecular Physiology and Biophysics. “We didn’t have a clear understanding of why that was happening.”

This sparked Galli and colleagues to investigate the link between insulin signaling and amphetamine action.

Using a rat model of type 1 – or juvenile – diabetes in which insulin levels are depleted, Galli’s group assessed the function of the dopaminergic pathway in the striatum, an area of the brain rich in dopamine.

In the absence of insulin, amphetamine-induced dopamine signaling was disrupted, they found. Dopamine release in the striatum was severely impaired and expression of DAT on the surface of the nerve terminal – where it normally acts to inactivate dopamine – was significantly reduced.

The lack of the protein on the plasma membrane prevents the amphetamine-induced increase in extracellular dopamine, and in turn, amphetamine fails to activate the dopamine pathways that stimulate reward, attention and movement, Galli noted.

The researchers then restored insulin by pulsing the hormone back into the brain of the diabetic animals and found that the system returns to

normal, indicating that the lack of insulin in the striatum directly affected amphetamine action.

To connect the physiological findings to activity in the intact brain, collaborators in the VUIIS, led by Avison, developed a probe for brain DAT activity using functional magnetic resonance imaging (fMRI).

“You can do molecular dissection in very well defined model systems and break the system down into its constituents,” said Avison, professor of Radiology and Radiological Sciences, and professor of Pharmacology. “But the question is: how does that relate to the intact brain? What’s the relevance to overall functioning in the intact system?”

Working with Galli and Avison, Jason Williams, Ph.D., used fMRI to demonstrate that in normal, healthy rats with plenty of insulin, amphetamine increased neural activity in the striatum. But in diabetic animals, activity in the striatum was suppressed.

“This finding is in vivo evidence that, in the intact diabetic rat, loss of insulin has compromised DAT trafficking to the plasma membrane,” Avison said. “These experiments show that there is likely a strong interplay between these important dopamine neurotransmitter systems and insulin signaling mechanisms, which we know are altered in diabetes”

The results are some of the first to link insulin status and dopaminergic brain function and hold several implications for human health and disease.

“This is really the first mechanistic connection in vivo between diabetes and amphetamine action,” Galli said. “This offers a completely new perspective on the influence of this disease (diabetes) on brain function, as well as diseases with altered dopamine signaling, such as

schizophrenia and ADHD."

The findings suggest that ADHD risk may have an insulin-dependent component and that control of insulin levels and response to the hormone may be an important determinant of amphetamine efficacy in patients with ADHD, Galli noted.

"We have described a novel mechanism by which diabetes may affect brain function."

Source: Vanderbilt University Medical Center