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Sticky blood protein yields clues to autism

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Many children with autism have elevated blood levels of serotonin – a chemical with strong links to mood and anxiety. But what relevance this "hyperserotonemia" has for autism has remained a mystery.

New research by Vanderbilt University Medical Center investigators provides a physical basis for this phenomenon, which may have profound implications for the origin of some autism-associated deficits.

In an advance online publication in the *Journal of Clinical Investigation*, Ana Carneiro, Ph.D., and colleagues report that a well-known protein found in blood platelets, integrin beta3, physically associates with and regulates the serotonin transporter (SERT), a protein that controls serotonin availability.

Autism, a prevalent childhood disorder, involves deficits in language, social communication and prominent rigid-compulsive traits. Serotonin has long been suspected to play a role in autism since elevated blood serotonin and genetic variations in the SERT have been linked to autism.

Alterations in brain serotonin have also been associated with anxiety, depression and alcoholism; antidepressants that block SERT (known as SSRIs, or selective serotonin reuptake inhibitors) block SERT's ability to sweep synapses clean of serotonin.

Working in the lab of Randy Blakely, Ph.D., Carneiro was searching for proteins that interact with SERT that might contribute to disorders where

serotonin signaling is altered.

“Levels of SERT in the brain are actually quite low, so we decided to see what progress we could make with peripheral cells that have much higher quantities,” said Blakely, the Allan D. Bass Professor of Pharmacology and director of the Vanderbilt Center for Molecular Neuroscience. “This took us to platelets.”

In platelets, SERTs accumulate serotonin produced in the gut. SSRIs or genetic deletion of SERT in animals prevents serotonin uptake in the platelet.

“Prior research had fingered the integrin beta3 gene as a determinant of blood serotonin levels and, independently, as a risk factor for autism,” Blakely said.

In the current study, Carneiro identified a large set of proteins that “stick” to SERT, presuming they might control SERT activity. One of these turned out to be integrin beta3.

Once they confirmed a physical relationship between the two proteins, Blakely’s team investigated whether the interaction can change SERT activity. They found that cells lacking integrin beta3 exhibit reduced serotonin uptake and that integrin beta3 activation or a human integrin beta3 mutation greatly enhances serotonin uptake.

“We found that integrin beta3 can put the serotonin transporter into high gear,” said Blakely. Notably, Edwin Cook, M.D., at the University of Illinois at Chicago and a co-author on the study, had shown that the same integrin beta3 mutation that elevates SERT activity also predicts elevated blood serotonin.

“Most investigators studying this integrin beta3 mutation have focused

on how its high activity state changes platelet clotting and never looked at its impact on serotonin levels or SERT function," explained Carneiro. "Now they have a reason to."

"We don't think the platelet itself contributes to autism," said Blakely, "but rather we believe that the brain's serotonin transporter may be controlled by integrin proteins in a very similar manner."

Carneiro and Blakely believe that too much SERT activity imposed by abnormal integrin interactions could restrict availability of serotonin in the brain during development, as well as in the adult.

"What is even more striking is that this is the second time we have found elevated SERT activity associated with autism," said Blakely. In a 2005 study, Blakely and Vanderbilt collaborator James Sutcliffe, Ph.D., identified mutations in the SERT gene that triggered elevated SERT activity.

Carneiro is now hot on the trail of integrin interactions with brain SERT as well as engineering mice that express human integrin beta3 mutations.

At a February Keystone Conference, Blakely described preliminary studies with mice that his lab has engineered to express hyperactive SERT mutations. "Together, these new animal models offer an unprecedented opportunity to peel away the complexity of autism and possibly develop new therapies," he said.

This research also may uncover new ways of treating depression. "Current antidepressant mechanisms still essentially work in the same way they did 25 years ago – by targeting transporter uptake of neurotransmitter directly," Carneiro said. "Now we may have a completely new way to go about it."

Source: Vanderbilt University Medical Center