Studies seek better understanding and treatment of depression

August 14 2012

Connecting the dots between two molecules whose levels are decreased in depression and increased by current antidepressants could yield new therapies, according to research by Dr. Anilkumar Pillai, neuroscientist at the Medical College of Georgia at Georgia Health Sciences University. Credit: Phil Jones, Georgia Health Sciences University Photographer

Connecting the dots between two molecules whose levels are decreased in depression and increased by current antidepressants could yield new therapies, researchers say.

Serotonin is a neurotransmitter that enables brain cells to communicate and brain-derived neurotropic factor, or BDNF, is a brain-nourishing

molecule that also aids connectivity. Popular antidepressants such as Prozac, developed to increase levels of serotonin, have recently been found to also increase BDNF levels, said Dr. Anilkumar Pillai, neuroscientist at the Medical College of Georgia at Georgia Health Sciences University.

"We don't know how the molecule, serotonin, which is well-studied in depression, regulates BDNF signaling," Pillai said. He's principal investigator on a five year, $1.5 million grant from the National Institute of Mental Health to help him make the connection

He suspects a critical piece is the protein transglutaminase 2, or TG2, expressed by brain cells and most other cell types. TG2 plays a role in natural serotonin recycling and potentially is a factor in the serotonin deficiency associated with depression. It also may help explain why levels of serotonin and BDNF seem to rise and fall in sync, Pillai said.

TG2 coverts serotonin to Rac1, a protein that helps rejuvenate BDNF receptors, which typically sit on the surface of brain cells but must periodically move inside to reinvigorate. Depression appears to upset the balance of these complex, critical inner workings. Pillai hypothesizes that the high levels he has found in depression, likely result in too much serotonin conversion leaving too little of the neurotransmitter to properly support brain cell communication. Instead, more Rac1 is produced but – inexplicably – its degradation also increases ultimately decreasing BDNF signaling as well.

Pillai has seen the unfortunate chain of events play out in an animal model with increased levels of TG2 and clear signs of depression. "If you can fix problems with the receptor, you should be able to reverse depressive symptoms in these mice," he said

One of the many questions he wants to answer is whether existing

antidepressants impact TG2. To help clarify the role of the impaired BDNF receptors, Pillai also wants to know whether giving BDNF to the depressed animal model improves depression. He's using a viral particle to directly activate the BDNF receptor. And he's also giving the TG2 inhibitor cysteamine to an animal model developed by administering stress hormones. He recently published in the journal PLoS ONE findings that the inhibitor appears effective in normalizing depressive behavior and BDNF levels in that model. Mental stress is a major factor in numerous psychiatric disorders including depression, schizophrenia and anxiety, he noted.

Some antidepressants, such as Prozac, were designed to interfere with a natural recycling of serotonin called reuptake so more serotonin is available where needed to enable cell communication. Pillai said it's not yet clear if serotonin reuptake is the same thing as its conversion to Rac-1.

"We need to learn more about how all these pieces fit to ultimately design new therapies for depression and related psychiatric disorders," he said. Dr. Alvin V. Terry Jr., MCG pharmacologist, is co-investigator on the studies.

Major depressive disorder is the leading cause of disability in Americans age 15-44, affects about 14.8 million adults and is more prevalent in women, according to the National Institute of Mental Health.

Provided by Georgia Health Sciences University