Shutting off neurons helps bullied mice overcome symptoms of depression

August 29 2013

A new drug target to treat depression and other mood disorders may lie in a group of GABA neurons (gamma-aminobutyric acid –the neurotransmitters which inhibit other cells) shown to contribute to symptoms like social withdrawal and increased anxiety, Penn Medicine researchers report in a new study in the *Journal of Neuroscience*.

Experts know that people suffering from depression and other mood disorders often react to rejection or bullying by withdrawing themselves socially more than the average person who takes it in strides, yet the biological processes behind these responses have remained unclear.

Now, a preclinical study, from the lab of Olivier Berton, PhD, an assistant professor in the department of Psychiatry, in collaboration with Sheryl Beck, PhD, a professor in the department of Anesthesiology at Children's Hospital of Philadelphia, found that bullying and other social stresses triggered symptoms of depression in mice by activating GABA neurons, in a never-before-seen direct relationship between social stimuli and this neural circuitry. Activation of those neurons, they found, directly inhibited levels of serotonin, long known to play a vital role in behavioral responses—without it, a depressed person is more likely to socially withdrawal.

Conversely, when the researchers successfully put the brake on the GABA neurons, mice became more resilient to bullying and didn't avoid once -perceived threats.

"This is the first time that GABA neuron activity—found deep in the brainstem—has been shown to play a key role in the cognitive processes associated with social approach or avoidance behavior in mammals," said Dr. Berton. "The results help us to understand why current antidepressants may not work for everyone and how to make them work better—by targeting GABA neurons that put the brake on serotonin cells."

Less serotonin elicits socially defensive responses such as avoidance or submission, where enhancement—the main goal of antidepressants—induces a positive shift in the perception of socio-affective stimuli, promoting affiliation and dominance. However, current antidepressants targeting serotonin, like SSRIs, are only effective in about 50 percent of patients.

These new findings point to GABA neurons as a new, neural drug target that could help treat the other patients who don't respond to today's treatment.

For the study, "avoidant" mice were exposed to brief bouts of aggression from trained "bully" mice. By comparing gene expression in the brains of resilient and avoidant mice, Berton and colleagues discovered that bullying in avoidant mice puts GABA neurons in a state where they become more excitable and the mice exhibit signs of social defeat. Resilient mice, however, had no change in neuron levels and behavior.

To better understand the link between GABA and the development of stress resilience, Berton, Beck, and colleagues also devised an optogenetics-based approach to directly manipulate levels: Lifting GABA inhibition of serotonin neurons reduced social and anxiety symptoms in mice exposed to bullies and also fully prevented neurobiological changes due to stress.

"Our paper provides a novel cellular understanding of how social defensiveness and social withdrawal develop in mice and gives us a stepping stone to better understand the basis of similar social symptoms in humans," said Berton. "This has important implications for the understanding and treatment of mood disorders."

Provided by University of Pennsylvania School of Medicine