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Riverside County, California

Study reveals new function for CACNA1C gene in psychiatric diseases

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A new study shows the death of newborn brain cells may be linked to a genetic risk factor for five major psychiatric diseases, and at the same time shows a compound currently being developed for use in humans may have therapeutic value for these diseases by preventing the cells from dying.

In 2013, the largest genetic study of psychiatric illness to date implicated mutations in the gene called CACNA1C as a risk factor in five major forms of neuropsychiatric disease -- schizophrenia, major depression, bipolar disorder, autism, and attention deficit hyperactivity disorder (ADHD). All the conditions also share the common clinical feature of high anxiety. By recognizing an overlap between several lines of research, scientists at the University of Iowa and Weill Cornell Medicine of Cornell University have now discovered a new and unexpected role for CACNA1C that may explain its association with these neuropsychiatric diseases and provide a new therapeutic target.

The new study, recently published in *eNeuro*, shows that loss of the CACNA1C gene from the forebrain of mice results in decreased survival of newborn neurons in the hippocampus, one of only two regions in the adult brain where new neurons are continually produced - a process known as neurogenesis. Death of these hippocampal neurons has been linked to a number of psychiatric conditions, including schizophrenia, depression, and anxiety.

"We have identified a new function for one of the most important genes in psychiatric illness," says Andrew Pieper, MD, PhD, co-senior author of the study, professor of psychiatry at the UI Carver College of Medicine and a member of the Pappajohn Biomedical Institute at the UI. "It mediates survival of newborn neurons in the hippocampus, part of the brain that is important in learning and memory, mood and anxiety."

Moreover, the scientists were able to restore normal neurogenesis in mice lacking the CACNA1C gene using a neuroprotective compound called P7C3-A20, which Pieper's group discovered and which is currently under development as a potential therapy for neurodegenerative diseases. The finding suggests that the P7C3 compounds may also be of interest as potential therapies for these neuropsychiatric conditions, which affect millions of people worldwide and which often are difficult to treat.

Pieper's co-lead author, Anjali Rajadhyaksha, associate professor of neuroscience in Pediatrics and the Feil Family Brain and Mind Research Institute at Weill Cornell Medicine and director of the Weill Cornell Autism Research Program, studies the role of the Cav1.2 calcium channel encoded by the CACNA1C gene in reward pathways affected in various neuropsychiatric disorders.

"Genetic risk factors that can disrupt the development and function of brain circuits are believed to contribute to multiple neuropsychiatric disorders. Adult newborn neurons may serve a role in fine-tuning rewarding and environmental experiences, including social cognition, which are disrupted in disorders such as schizophrenia and autism spectrum disorders," Rajadhyaksha says. "The findings of this study provide a direct link between the CACNA1C risk gene and a key cellular deficit, providing a clue into the potential neurobiological basis of CACNA1C-linked disease symptoms."

Several years ago, Rajadhyaksha and Pieper created genetically altered mice that are missing the CACNA1C gene in the forebrain. The team discovered that the animals have very high anxiety.

"That was an exciting finding, because all of the neuropsychiatric diseases in which this gene is implicated are associated with symptoms of anxiety," says Pieper who also holds appointments in the UI Departments of Neurology, Radiation Oncology, Molecular Physiology and Biophysics, the Holden Comprehensive Cancer Center, and the Iowa City VA Health Care System.

By studying neurogenesis in the mice, the research team has now shown that loss of the CACNA1C gene from the forebrain decreases the survival of newborn neurons in the hippocampus - only about half as many hippocampal neurons survive in mice without the gene compared to normal mice. Loss of CACNA1C also reduces production of BDNF, an important brain growth factor that supports neurogenesis.

The findings suggest that loss of the CACNA1C gene disrupts neurogenesis in the hippocampus by lowering the

production of BDNF.

Pieper had previously shown that the "P7C3-class" of neuroprotective compounds bolsters neurogenesis in the hippocampus by protecting newborn neurons from cell death. When the team gave the P7C3-A20 compound to mice lacking the CACNA1C gene, neurogenesis was restored back to normal levels. Notably, the cells were protected despite the fact that BDNF levels remained abnormally low, demonstrating that P7C3-A20 bypasses the BDNF deficit and independently rescues hippocampal neurogenesis.

Pieper indicated the next step would be to determine if the P7C3-A20 compound could also ameliorate the anxiety symptoms in the mice. If that proves to be true, it would strengthen the idea that drugs based on this compound might be helpful in treating patients with major forms of psychiatric disease.

"CACNA1C is probably the most important genetic finding in psychiatry. It probably influences a number of psychiatric disorders, most convincingly, bipolar disorder and schizophrenia," says Jimmy Potash, MD, professor and DEO of psychiatry at the UI who was not involved in the study. "Understanding how these genetic effects are manifested in the brain is among the most exciting challenges in psychiatric neuroscience right now."

Source:
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