New insights into lithium's effectiveness for bipolar disorder

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Bipolar disorder is characterized by transitions between depression and mania. Credit: Wikipedia

Bipolar disorder, a neuropsychiatric condition that includes manic and

depressive episodes, affects about 1% of the population and is strongly influenced by genetics. About half of patients respond very well to lithium salts as a therapy, and treatment responsiveness also depends on genetics. Researchers still have little idea of how lithium works to stabilize mood, but, similar to other anti-depressants, it stimulates proliferation of adult neural progenitor cells (NPC), perhaps leading to the birth of new neurons. Now, a new study identifies a specific gene that seems to regulate NPC proliferation in response to lithium.

The study, led by Jason Stein, Ph.D., at The University of North Carolina at Chapel Hill, appears in *Biological Psychiatry*.

"Some people with bipolar disorder show therapeutic responses to lithium, while others do not," said Dr. Stein.

"Previous studies have identified a limited number of genetic variations contributing to lithium's clinical outcomes. These studies are incredibly important, but are also costly, require large sample sizes, and do not identify cell types or biological processes mediating genetic effects. Here, we took an alternative approach by performing a genome-wide association study (GWAS) in a cell culture system from multiple human donors, either exposed to or not exposed to lithium."

To measure lithium-induced neural proliferation, the researchers employed a cell culture of human NPCs obtained from fetal brain tissue. Some cultures were exposed to lithium, which increased cell proliferation, whereas other cultures were not. The authors then performed GWAS tests.

"Our cell-culture based GWAS approach identified genetic variation as well as a specific gene that influenced lithium-responsive neural progenitor proliferation," said Dr. Stein.

John Krystal, MD, editor of *Biological Psychiatry*, said of the study that "the efficacy of lithium remains one of the great mysteries in psychiatry. Emerging from an accidental discovery, it remains a wonder drug for many patients. This study identifies mechanisms underlying the ability of lithium to stimulate proliferation of neural progenitor cells. In particular, they implicate chromosome 3p21.1 and the guanine nucleotide-binding protein-like 3 (GNL_3) gene in this effect. GNL_3 has been implicated previously in cell cycle regulation and cellular differentiation."

GNL_3 has also been implicated in risk for bipolar disorder, schizophrenia and inter-individual variations in intelligence, suggesting the gene plays an important role in brain function.

Using CRISPR technology, the researchers then increased expression of GNL_3 in the cultures, which in turn increased neural proliferation in response to lithium. Conversely, decreasing expression of GNL_3 decreased lithium-induced proliferation.

"Though more experiments are required to determine if these results have clinical potential, this study opens up a new approach of identifying pharmacogenomic effects in cell culture systems," added Dr. Stein.

More information: Justin M. Wolter et al, Cellular genome-wide association study identifies common genetic variation influencing lithium induced neural progenitor proliferation, *Biological Psychiatry* (2022). DOI: 10.1016/j.biopsych.2022.08.014