Researchers Discover How Lithium Works

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Despite more than 30 years of widespread use of lithium to control psychiatric disorders, such as bipolar disorder, scientists have been uncertain about how this drug actually works on a molecular level.

However, in a paper published in the January 11th issue of *Cell,* a Duke Medical Center team has found that lithium may alleviate manic and depressive-like behaviors by interrupting the signaling of a dopamine receptor in the brain. The team was led by Marc G. Caron, Ph.D., James B. Duke Professor in the Department of Cell Biology, Medicine and Neurobiology, and Martin Beaulieu, Ph.D., now at Université Laval.

Over the years, lithium has been shown to act principally on two targets in the brain. It is known to inhibit enzymes that maintain a signaling pathway from the cell membrane. And it inhibits an enzyme called glycogen synthase kinase 3 (GSK-3), which is important in the cell's response to many signaling molecules. But, whether these targets are important for the therapeutic effects of lithium has been unclear.

Caron and Beaulieu previously showed that one of the dopamine receptors in the brain, the D2 receptor, transmits its signal by engaging a pathway involving GSK-3. The D2 receptor regulates this pathway with a signaling complex made up of the receptor and enzymes held together by a protein called beta-arrestin 2.

When placed in a new environment, mice genetically engineered to have an overactive dopamine system typically run around frantically. Similar hyperactivity and mania-like state can be seen in mice treated with

amphetamines. Previous research by Caron and Beaulieu had shown that treatment with lithium calms these mice by interfering with the D2 receptor/GSK3 pathway. Caron and his colleagues set out to investigate how lithium produced these effects.

"In humans, lithium alleviates the mood swings and excitability characteristic of bipolar disorder. However, the concentrations at which lithium is clinically effective are usually lower that those necessary to affect the presumed targets like GSK3 in preclinical studies. So there had to be another mechanism," said Caron.

The team focused on whether lithium was acting on the beta-arrestin signaling complex after finding that in another line of genetically engineered mice lacking the gene for the beta-arrestin 2 protein, many of the actions of the D2 receptor were absent.

"We found that lithium destabilizes the signaling complex necessary for the D2 receptor to engage the GSK3 signaling pathway," said Beaulieu, the lead author of the study. In the mice that lack beta-arrestin 2, the researchers found that lithium had no effects on a number of mouse behaviors thought to correlate with symptoms of depression and mania in humans.

"We found that the destabilizing effects of lithium on this signaling complex are observed at concentrations of lithium that are in the range of the clinically effective doses used in the treatment of humans," said Caron, the senior author of the study.

Over the past several years, studies by another contributor to this study, Robert J. Lefkowitz, James B. Duke Professor and HHMI Investigator at Duke, have shown that many other receptorss, similar to D2 receptors, can signal through the formation of complexes organized by the protein beta-arrestin 2.

The researchers propose that targeting these beta-arrestin signaling complexes might be an effective target to control cell signaling. "We feel that this mechanism is a new principle of pharmacology and could lead to drugs for a host of disorders," said Caron.

Source: Duke University Medical Center

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