Drosophila drug screen for fragile X syndrome finds promising compounds and potential drug targets

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Scientists using a new drug screening method in Drosophila (fruit flies), have identified several drugs and small molecules that reverse the features of fragile X syndrome -- a frequent form of mental retardation and one of the leading known causes of autism. The discovery sets the stage for developing new treatments for fragile X syndrome.

The results of the research by lead scientist Stephen Warren, PhD, chair of the Department of Human Genetics at Emory University School of Medicine, are published online in the journal *Nature Chemical Biology*.

Dr. Warren led an international group of scientists that discovered the FMR1 gene responsible for fragile X syndrome in 1991. Fragile X syndrome is caused by the functional loss of the fragile X mental retardation protein (FMRP). Currently there is no effective drug therapy for fragile X syndrome, and previously no assays had been developed to screen drug candidates for the disorder.

During the past 17 years, intense efforts from many laboratories have uncovered the fundamental basis for fragile X syndrome. Scientists believe FMRP affects learning and memory through regulation of protein synthesis at synapses in the brain. One leading view, proposed by Dr. Warren and colleagues, suggests that over stimulation of neurons by the neurotransmitter glutamate is partly responsible for the brain dysfunction resulting from the loss of FMRP.

In their current experiment, Emory scientists used a Drosophila model lacking the FMR1 gene. These fruit flies have abnormalities in brain architecture and behavior that parallel abnormalities in the human form of fragile X syndrome. When FMR1-deficient fly embryos were fed food containing increased levels of glutamate, they died during development, which is consistent with the theory that the loss of FMR1 results in excess glutamate signaling.

The scientists placed the FMR1-deficient fly embryos in thousands of tiny wells containing food with glutamate. In addition, each well contained one compound from a library of 2,000 drugs and small molecules. Using this screening method, the scientists uncovered nine molecules that reversed the lethal effects of glutamate.

The three top identified compounds were known activators of GABA, a neural pathway already known to inhibit the effects of glutamate. In the study, GABA reversed all the features of fragile X syndrome in the fruit flies, including deficits in the brain's primary learning center and behavioral deficits. The screening also identified other neural pathways that may have a parallel role in fragile X syndrome and could be targets for drug therapy.

"Our discovery of glutamate toxicity in the Drosophila model of fragile X syndrome allowed us to develop this new screen for potential drug targets," notes Dr. Warren. "We believe this is the first chemical genetic screen for fragile X syndrome, and it highlights the general potential of Drosophila screens for drug development.

"Most importantly, it identifies several small molecules that significantly reverse multiple abnormal characteristics of FMR1 deficiency. It also reveals additional pathways and relevant drug targets. These findings open the door to development of effective new therapies for fragile X syndrome."

Source: Emory University