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Researchers Design Cells to Help Determine Workings of Drugs

GEN News Highlights

Scientists at the [University of California, San Diego](#) (UCSD) have come up with a method that helped them figure out how atypical neuroleptics, used to treat schizophrenia, work. Quoc-Thang Nguyen, Ph.D., co-lead author of the research, recently founded Femtoscience, which has licensed the technology and will develop it as a way to screen drugs.

The technique is detailed in *Nature Neuroscience* in a paper titled “An in vivo biosensor for neurotransmitter release and in situ receptor activity.”

Atypical neuroleptics elicit large releases of the neurotransmitter acetylcholine. They have also been shown to barricade a particular type of receptor on the receiving cell's surface, which would block the message. The question that has plagued researchers is which action prevails.

To find out the team designed biological cells that change color when acetylcholine latches onto this particular class of receptors, called M1. That allowed them to see when M1 receptors received the chemical message, an event neuroscientists had previously been unable to detect in a living brain. “It's a world of signaling between cells that we were blind to before,” points out David Kleinfeld, Ph.D., professor of physics and member of UCSD's center for neural circuits and behavior, who led the collaboration that invented the system.

The team developed cells, which they call cell-based neurotransmitter fluorescent-engineered reporters (CNiFERS), to monitor in situ neurotransmitter receptor activation. CNiFERS are cultured cells that are engineered to express a chosen metabotropic receptor, use the Gq protein-coupled receptor cascade to transform receptor activity into a rise in cytosolic, and report with a genetically encoded fluorescent Ca²⁺ sensor.

The team implanted the cells in rat brains and then stimulated a deeper part of the brain in a way known to release acetylcholine nearby. They saw a color change, evidence that the CNiFERS were working. Then they gave the rats one of two atypical neuroleptics. In both cases, the drug severely depressed the response, indicating that the drugs' receptor-blocking action overrides the increase in acetylcholine.

The scientists are currently designing CNiFERS to detect the activity of other types of receptors as well. “The technique puts CNiFERS together from easily obtained molecular components,” explains Dr. Nguyen.