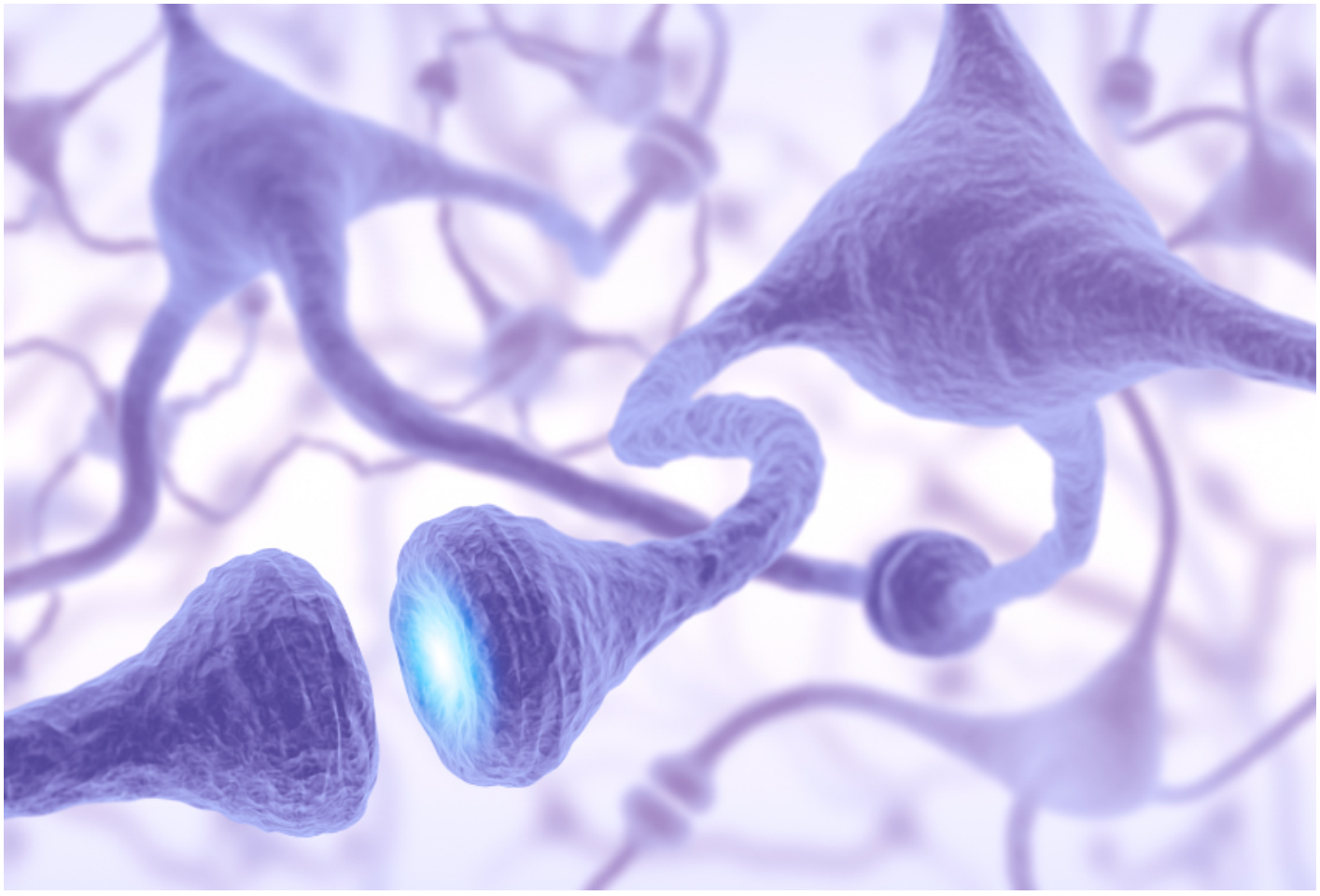
TOOLBOX

Molecular switch lets light shut off subsets of brain signals

BY **NICHOLETTE ZELIADT**

16 DECEMBER 2015



A tool kit of light-sensitive proteins allows researchers to mute communication between specific sets of neurons in mice. The kit, described 2 December in *Neuron*, could help to clarify the role of these neuronal circuits, which relay messages through the molecule gamma-aminobutyric acid

(GABA), in autism[1].

GABA dampens brain activity by binding to a diverse group of channels that span the membranes of some neurons. This binding causes the channels to open, flooding neurons with negatively charged chloride ions and suppressing their activity.

Several lines of evidence link altered GABA signaling to autism: Some people with the condition have **low levels of GABA**, and some carry mutations in **GABA receptor genes**.

Scientists can study GABA signaling using drugs that activate or inhibit GABA receptors, or with 'optogenetics,' which uses light to boost or suppress neural activity. But neither technique can manipulate the function of only a specific subtype of GABA receptors, built from a set combination of subunits.

The new approach is a variation on optogenetics. Researchers devised a strategy that uses light to rapidly and precisely control specific GABA receptor types.

Light switch:

The researchers created mutant versions of the GABA receptor subunits that stick to a synthetic molecule, rendering them light-sensitive. Flashes of green light cause the synthetic compound to change shape, blocking GABA from binding the receptor. This essentially turns the receptors off. Flashes of violet light cause the molecule to revert to its original shape, allowing GABA to once again bind and activate the receptors.

Using this technique blocks up to 80 percent of GABA receptor activity in cultured rat neurons and brain slices. Flashes of light as short as 100 milliseconds can toggle the receptor between its two states.

The researchers then delivered GABA to precise sites along the neuron and measured changes in neural activity. This experiment revealed that one receptor type is concentrated at **synapses** — hubs of communication between neurons. Another type is dispersed throughout the cell.

Next, the scientists engineered mice with light-sensitive GABA receptors and bathed the entire cerebral cortex — the surface of the brain — with light as the mice watched a video with alternating black and white bars. The researchers found that the rate of neuron firing in vision centers of the brain increases when GABA receptors are turned off.

They are working on a way to turn GABA receptors on. They have also found that the synthetic molecule appears to be specific to the GABA mutants.

REFERENCES:

1. Lin W.C. *et al. Neuron* **88**, 879-891 (2015) **PubMed**