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Conducting how neurons fire

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Figure 1: Changing a neuron's membrane conductance of ions can switch its response to a neurotransmitter from excitation to inhibition. © 2011 Alexey Semyanov

Contrary to expectations that the neurotransmitter GABA only inhibited neuronal firing in the adult brain, RIKEN-led research has shown that it can also excite interneurons in the hippocampus of the rat brain by changing the conductance of ions across the membranes of these cells.

According to conventional wisdom, activation of the GABAA receptor subtype at the communication junction between neurons—the synapse—strongly increases membrane conductance of ions, triggering a process called shunting, which inhibits neuronal firing. Led by Alexey

Semyanov of the RIKEN Brain Science Institute in Wako, Japan, the team demonstrated that activation of these receptors outside of synaptic junctions, so-called 'extrasynaptic receptors' can also excite the neurons.

Further activation of these extrasynaptic receptors by application of higher concentrations of GABA turn excitation into inhibition (Fig. 1). "To our knowledge, this is the first demonstration that changes in membrane conductance can switch the action of a neurotransmitter from excitation to inhibition," Semyanov says.

Semyanov and colleagues treated slices of the mouse hippocampus with low or high concentrations of GABA and compared the effects. They showed that the more GABA they added, the more they could detect an increase in the conductance of the membranes of hippocampus cells called CA1 interneurons. The increased conductance was mediated through extrasynaptic GABAA receptors.

The CA1 interneurons could spontaneously fire action potentials—electrical impulses that transfer signals in the network of interconnected neurons. Adding low concentrations of GABA increased the rate of action potential firing, while high concentrations of GABA reduced action potential firing in the cells. Because the concentration of GABA that slowed neuronal firing had also enhanced membrane conductance, the researchers argue that increasing this conductance by activating extrasynaptic GABAA receptors can result in inhibition via shunting along the membrane, which would cause a decrease in action potential generation in the neurons.

The hippocampus plays a key role in learning and memory, and GABA concentrations are known to increase in this part of the brain during exploratory behavior in rats. The findings therefore raise the intriguing possibility that changes in GABA concentration in the brain during some behavioral tasks could bidirectionally change neuronal excitability; this

could be a characteristic of the hippocampal neuronal network that may be required for some behavioral tasks in animals.

“Many clinically used drugs, such as sedatives or anti-epileptics, target GABA receptors,” notes Semyanov. “Our findings could potentially explain their therapeutic action as well as some of their unwanted side effects.”

More information: Song, I., Savtchenko, L. & Semyanov, A. Tonic excitation or inhibition is set by GABAA conductance in hippocampal interneurons. *Nature Communications* 2, 376 (2011). www.nature.com/ncomms/journal/ … /abs/ncomms1377.html

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