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Electrical activity in developing brain influences choice of neurotransmitter

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Cascades of genetic signals determine which neurotransmitter a brain cell will ultimately use to communicate with other cells. Now a pair of reports from biologists at the University of California, San Diego, have shown for the first time that electrical activity in these developing neurons can alter their chemical fate—and change an animal's behavior—by tweaking this genetic program.

"When I was a graduate student we were taught that the transmitters that neurons use were fixed and unchanging. It's now clear that the electrical activity of the nervous system that we use for rapid communication also has the effect of changing the transmitters that neurons make and use," said Nicholas Spitzer, a professor in the Division of Biological Sciences who leads the research group that made the discoveries. The studies, which looked at two different transmitter systems, will appear in the August issues of the journals *Neuron* and *Nature Neuroscience*.

Michaël Demarque, a post-doctoral fellow in Spitzer's lab, looked at the development of neurons in the hindbrain of the African clawed frog Xenopus laevis. By the time embryonic frogs have sprouted a tail bud, some of these neurons have already adopted the neurotransmitter serotonin. Others have adopted different neurotransmitters. Although none of them are connected to other neurons, they generate periodic spikes of positively charged calcium ions within the cell that last for seconds and occur a few times each hour.

By altering the frequency of those electrical signals, Demarque could

change the number of neurons that used serotonin. Dampening the calcium spikes increased the number of neurons expressing a particular gene, Lmx1b, with two subsequent effects. More of the neurons in that part of the brain began to make serotonin, and the behavior of the tadpoles changed as well. When placed in a round dish and poked on the tail, tadpoles with more serotonin neurons swam fewer laps before settling down, Demarque and Spitzer report in *Neuron*.

"Our work illustrates how the environment in which development takes place could affect the maturation of the nervous system," Demarque said. Changes in serotonin function have been implicated in human disorders such as anxiety, depression and autism, highlighting the importance of understanding the developmental pathways that shape the system, the authors wrote.

Post-doctoral fellow Kurt Marek and graduate student Lisa Kurtz, also in Spitzer's lab, found a similar relationship between electrical activity and specification of neurotransmitter in a different neural system, and they were able to pin down the fine details of the molecular interaction, they report in Nature Neuroscience.

In a different species of African clawed frog, Xenopus tropicalis, they looked at neurons in the embryonic spinal cord at a point in development when the choice is between a neurotransmitter that is excitatory, making the neurons it contacts more likely to fire an electrical impulse, or one that is inhibitory.

They found that electrical activity influences development through a genetic switch called tlx3, which determines whether a cell will use the neurotransmitter glutamate, which is excitatory or GABA, which is inhibitory. They also identified a specific molecule that responds to calcium spikes by controlling the activity of the gene.

"We have a molecular pathway connecting calcium activity to a genetic switch that can completely reverse the polarity of the circuit," Marek said.

Both genetic factors and activity determine which neurotransmitter the mature neuron will use, an interaction that likely allows the brain to assemble circuits appropriate to a variable environment, the authors wrote.

Provided by University of California - San Diego