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Low-dose sedative alleviates autistic-like behavior in mice with Dravet syndrome mutation

August 22 2012

A low dose of the sedative clonazepam alleviated autistic-like behavior in mice with a mutation that causes Dravet syndrome in humans, University of Washington researchers have shown.

Dravet syndrome is an infant seizure disorder accompanied by developmental delays and behavioral symptoms that include autistic features. It usually originates spontaneously from a gene mutation in an affected child not found in either parent.

Studies of mice with a similar gene mutation are revealing the overly excited brain circuits behind the autistic traits and cognitive impairments common in this condition. The research report appears in the Aug. 23 issue of *Nature*. Dr William Catterall, professor and chair of pharmacology at the UW, is the senior author.

Dravet syndrome mutations cause loss-of-function of the human gene called SCN1A. People or mice with two copies of the mutation do not survive infancy; one copy results in major disability and sometimes early death. The mutation causes malformation in one type of sodium ion channels, the tiny pores in nerve cells that produce electrical signals by gating the flow of sodium ions.

The Catteralll lab is studying these defective ion channels and their repercussion on cell-to-cell signaling in the brain. They also are

documenting the behavior of mice with this mutation, compared to their unaffected peers. Their findings may help explain how the sporadic gene mutations that cause Dravet syndrome lead to its symptoms of cognitive deficit and autistic behaviors.

The sodium ion channels in question malfunction in specific nerve cells, called inhibitory neurons, whose job is to send messages to hush the electrical signaling of neighboring cells. If only transmissions that excite nearby cells get through, the balance of cell signals that excite or inhibit the brain is seriously tilted toward excessive excitability.

"Imagine New York City traffic without any red lights, just green lights," said Catterall. This kind of electrical traffic jam might explain the heightened brain state of children with the Dravet mutation. These children suffer from frequent electrical storms, called epileptic seizures, in their brains. They are hyperactive, anxious and have difficulty sleeping. Their problems in learning, remembering and reasoning often follow a downhill course through childhood. The children also show several symptoms of an autistic spectrum disorder, including withdrawing from social interactions, repeated movements, and restricted, intense interests. The brain mechanisms behind this disorder have been poorly understood, Catterall said.

In observing the behavior of mice with the same genetic variation, Catterall and his team saw that they did not display many normal social interactions of mice. Mice are naturally curious about a mouse they haven't met before, and will approach and sniff it. Sometimes they will attack, wrestle and playfully bite the stranger. Usually mice are more interested in mice they haven't met before than those they already know. Mice with the Dravet syndrome were not interested in meeting strangers or acknowledging acquaintances, and did not approach them either aggressively or with mild manners. In fact, they froze when confronted with new mice, the scent of male mouse urine, or new food smells like

banana oil, which usually attracts mice unfamiliar with the scent.

These altered behaviors suggested that the Dravet mice were unable to have normal social interactions with recently introduced mice and were repelled by new experiences, even new food odors. The Dravet mice also had problems in spatial learning and memory. They were unable to learn and remember the location where fearful events occurred or to learn and remember how to escape a brightly lighted area. In an open field test and maze running comparisons with mice without the mutation, the Dravet mice traveled more, spend less time in the center, and walked in circles. They also groomed themselves and wiped their whiskers excessively.

"Like many children with autism, the mice seemed overwhelmed by changes in their environment and unable to interact socially with other mice," Catterall said. "They also showed stereotypic movements and repetitive behaviors common in autism."

His team went on to explore the cellular and biochemical underpinnings of the autism-related traits and spatial learning deficits in the Dravet mutation mice. They tested the hypothesis that the condition arises from decreased activity of particular sodium ion channels in the brain cells that relay inhibitory information to other nerve cells in the forebrain.

They found that the deep layer of the prefrontal cortex of the brain was the most affected by the mutation. Among the core components linking thinking and emotion circuits of the brain are the interneurons. These cells release a neurotransmitter called GABA, a brain chemical signal that inhibits neighboring cells. On the other hand, excitatory nerve cells release a different neurotransmitter that activates neighboring nerve cells. Normally, these excitatory and inhibitory nerve cells balance each other.

The researchers found that the Dravet mutation mice had the normal

number of the GABAergic interneurons, the cells that fire a "turn it down" signal to their neighbors. However, a significant percentage of these cells lacked a specific type (type-1 or Nav1.1) of gated sodium channel. This deficit kept these cells from firing enough electrical signals. As a consequence, excitatory signals dominated circuits in critical areas of the brain.

"We reasoned that the decreased in sodium channel activity in these GABAergic interneurons could be rescued by increasing the strength of the GABAergic transmissions," Catterall said.

His team decided to treat both the normal and the Dravet mutation mice with the benzodiazepine clonazepam. This drug is often given to people suffer from moderate, debilitating anxiety, such as fear of flying. Benzodiazepines also control some forms of epileptic seizures. The researchers lowered the dose to make sure they were not sedating the mice or removing their anxious state.

"The treatment with a single low dose of clonazepam completely alleviated the impaired social interactions of the Dravet mice. It also removed the freezing reaction to novel situations. They were willing to approach mice that were strangers to them and to explore new odors. They behaved just like their peers," Catterall observed. "This dose of the drug had no effect on the behavior of their normal peers." The effects of the drug wore off after it cleared completely from the body, which takes a few days in mice.

"The results showed that a single low dose of clonazepam can reversibly rescue core autistic traits and cognitive deficits in mice with the Dravet mutation," Catterall said. Additional measurements of cell firing in brain tissues from affected mice showed that the behavioral effects were likely based on decreased strength of the inhibitory signals, which caused an overall increase in brain electrical signaling by releasing the restraint

on excitatory neurons. Their research also suggested that the cognitive and behavioral impairments in Dravet syndrome are not the result of damage from epileptic seizures, but are due to an innate shortage of a certain type of sodium ion channel and the resulting failure of inhibitory electrical signaling.

Catterall added that the research indicates that low-dose benzodiazepine treatment could be a potential drug intervention for cognitive deficits and autistic symptoms in Dravet syndrome patients, if clinical trials show they are effective in humans, and perhaps more broadly in certain other types of autism spectrum disorders.

"Interestingly, mutations in many other autism spectrum disorders also cause an imbalance of excitatory over inhibitory electrical activity in the brain," the research team noted. Perhaps autistic traits in some other conditions within the realm of autism spectrum disorders might also be caused by a reduction in GABAergic signaling between brain cells.

Dravet syndrome is not the only genetic disorder that has autistic traits accompanying other physical and developmental disabilities. Rett, fragile X, and Timothy syndromes also have autistic features.

More information: DOI: 10.1038/nature11356

Provided by University of Washington