TIME IN PARTNERSHIP WITH CNN

Thursday, Apr. 29, 2010

Obsessively Groomed Mice: A Gene Link to OCD

By Jeffrey Kluger

It's hard to picture a mouse with mental health issues, but in their own tiny way, mice can suffer from at least one psychiatric condition: obsessive-compulsive disorder (OCD). Thanks to a new discovery from Weill Cornell Medical College in New York City, scientists may now be able to use that fact to help humans struggling with the same debilitating condition.

The Weill Cornell team, headed by molecular biologists Dr. Shahin Rafii, Dr. Francis Lee and Dr. Sergey Shmelkov, had not initially set out to study OCD. Instead, they were conducting research on the role of a gene known as Slitrk5 in the development of stem cells that eventually specialize into blood cells. To understand the function of the gene better, they engineered mice in which Slitrk5 was disabled (or "knocked out"). They then looked for how it affected the animals' bloodstream. The verdict: it didn't. (See how to live 100 years.)

But that didn't mean the mice were unchanged. Before long, the knockout mice began developing curious lesions around their mouths. In addition, they became unusually anxious and jumpy — even by mouse standards. On closer examination, the mice appeared to be engaging in hyperactive grooming behavior, far more than normal mice do and more than enough to cause the facial injury they were suffering.

Other species of animals have been known to display similarly excessive grooming behaviors. Parrots compulsively pluck their own feathers; dogs repetitively lick a paw or other fixed spot; humans develop a condition known as trichotillomania, in which they pull out strands of their hair. All of these behaviors are thought to fall along the OCD spectrum, though of course the disorder is much more complex in humans. It's characterized by intrusive, obsessive thoughts (fear of being contaminated by germs, for instance, or anxiety about whether the door is locked) and compulsive behaviors intended to relieve the anxiety caused by those obsessions (hand-washing, counting and other repetitive behaviors). (See how to prevent illness at any age.)

Intrigued by what they had found, the Weill Cornell team tried Prozac on their mice — the antidepressant can help relieve symptoms in humans and, in some experiments, dogs — and found that it did eliminate the grooming behavior in the rodents. What's more, studies of the mouse brains revealed trademark patterns in the neural wiring between the frontal lobes and the striatum, which also turns up in human OCD patients. "This is an unexpected offshoot from stem cell science to the realm of psychiatry," said Rafii in a statement. "[It] could have major application for neuropsychiatric disease." (Comment on this story.)

But how, exactly? Mice aren't people, and while lab animals can be good biological templates for human

beings, they're hardly perfect ones — particularly when it comes to complex behaviors. What's more, as molecular biologists know, there are few diseases or disorders caused by a single gene. At best, Slitrk5 may turn out to be just one of many genes that interact and contribute to obsessive-compulsive disorder in untold ways.

Still, Slitrk5 does appear to be a doozy. The gene, which exists in humans as well as in mice, appears to plays a role in the release and uptake of glutamate in the brain, a neurotransmitter that helps regulate urges. In the knockout mice, researchers found the greatest irregularities in the frontal cortex and the striatum — the gene was excessively active in one part of the frontal cortex, while the level of glutamate receptors in the striatum was decreased. In humans, the frontal cortex–striatum circuit is involved in laying down memories and processing rewards that may later guide the planning and control of behavior; it makes sense that dysfunction here could be related to the uncontrollable urges and behaviors of OCD. Earlier studies have also linked variations on the Slitrk5 gene to Tourette's syndrome, a condition characterized by involuntary tics, vocalizations and even shouting of obscenities. Some doctors place Tourette's along the OCD spectrum too — though admittedly at a far end.

The new study isn't the first time to make the glutamate-OCD connection in a mouse. In August 2007, scientists led by neurobiologist Jeffrey Welch at Duke University Medical Center engineered mice with a different gene knocked out, this one responsible for producing a sort of protein scaffold found in synapses involved in glutamate transmission — and is highly expressed in the striatum. Here too the altered mice engaged in compulsive behavior, and here too Prozac-type drugs helped relieve the symptoms.

Mouse models of OCD, however basic, could someday help develop better treatments for people — especially those who do not respond well to medication or to cognitive-behavioral therapy. By looking for protein markers of Slitrk5 in the blood, or hyperactive behaviors consistent with the form of OCD linked to that gene, doctors could begin therapy earlier and target it more precisely. "You could break OCD into subsets the same way pneumonia was originally broken into bacterial or viral categories," Lee tells TIME.

It may be possible, then, to treat the right subset by developing a drug that neutralizes or in some other way alters the expression of the Slitrk5 protein. "We could deliver this through the blood," says Rafii. "We can talk to the neuronal cell by using a surface receptor." Even if that didn't work, the protein is not an end in itself. The way it interacts with cells produces other molecules further downstream that could themselves be neutralized or blocked.

None of this, of course, makes much difference to the mice, who rarely develop anything like OCD unless scientists fool with their genes in the first place. But for the 3 million adults and 500,000 children who suffer from the condition in the U.S., any new glimmer — no matter the source — is a welcome one.

See TIME's Pictures of the Week.

See the Cartoons of the Week.

Click to Print

Find this article at:
http://www.time.com/time/health/article/0,8599,1985244,00.html