SOUTHWESTERN NEWS

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'Smart' mice teach scientists about learning process, brain disorders

DALLAS – May 27, 2007 – Mice genetically engineered to lack a single enzyme in their brains are more adept at learning than their normal cousins, and are quicker to figure out that their environment has changed, a team led by researchers at UT Southwestern Medical Center has found.

The results, appearing today in the online edition of the journal *Nature Neuroscience*, reveal a new mechanism of learning in the brain, which might serve in humans as a target for treating disorders such as post-traumatic stress disorder, Alzheimer's disease or drug addiction, the researchers said.

"It's pretty rare that you make mice 'smarter,' so there are a lot of cognitive implications," said Dr. James Bibb, assistant professor of psychiatry and the study's senior author.

"Everything is more meaningful to these mice," he said. "The increase in sensitivity to their surroundings seems to have made them smarter."

The engineered mice were more adept at learning to navigate a water maze and remembering that being in a certain box involves a mild shock. Equally important, Dr. Bibb said, when a situtation changed, such as the water maze being rearranged, the engineered mice were much faster to realize that things were different and work out the new route.

Dr. Bibb cautioned that while the mice learn faster, studies on the long-term effects of deleting the enzyme, called Cdk5, from the brain are continuing.

The group is also beginning a search for drugs that might create the same effects without genetic manipulation and monitoring the animals' health and behavior over time.

The findings may have applications in treating post-traumatic stress disorder, where getting a patient to learn that a once-threatening situation no longer poses a danger is a major goal.

In addition, Cdk5 is heavily implicated in Alzheimer's disease and addiction to drugs of abuse, so understanding how the enzyme affects the brain and behavior might aid in the development of new treatments for these and other conditions, Dr. Bibb said.

The key in this study was being able to "knock out" the gene for Cdk5 only in the brain, and only when the mice were adults. This technique, only recently developed and called conditional

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knockout, allows much more sophisticated experiments than traditional knockout, which entirely eliminates the gene.

"Being able to turn a gene off throughout a brain is a really advanced thing to do," Dr. Bibb said. "It's been shown that it *can* be done, but we put the system together and actually applied it."

Normally, Cdk5 works with another enzyme to break up a molecule called NR2B, which is found in nerve-cell membranes and stimulates the cell to fire when a nerve-cell-signaling molecule, or neurotransmitter, binds to it. NR2B previously has been implicated in the early stages of learning.

The new research showed that when Cdk5 is removed from the brain, the levels of NR2B significantly increase, and the mice are primed to learn, Dr. Bibb said.

"We made the animals 'smarter,' but in doing so and applying this technology, we also found biochemical targets that hold promise for future treatments of a variety of cognitive disorders," he said.

The researchers also recorded nerve-cell firings in the hippocampus, an area of the brain associated with learning. Hippocampus slices from the knock-out mice responded much more strongly to an electrical stimulation, supporting the finding that the mice were more prepared to learn.

Other UT Southwestern researchers involved in the study were Ammar Hawasli, David Benavides and Chan Nguyen, students in the Medical Scientist Training Program; Dr. Janice Kansy, instructor in psychiatry; Dr. Kanehiro Hayashi, postdoctoral researcher in psychiatry; Dr. Craig Powell, assistant professor of neurology; and Dr. Donald Cooper, assistant professor of psychiatry. Researchers from the Institut de Génétique et de Biologie Moléculaire et Cellulaire in Strausbourg, France, and The Rockefeller University also participated.

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