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Making Smart Mice

Lab-bred "Doogie" mice learn faster and remember more than their field-born brethren
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Scientists may not be able to build a better mouse trap, but they have learned how to build a better mouse. Princeton neurobiologist Joe Z. Tsien and colleagues from MIT and the University of Washington recently created a strain of brainier mice, dubbed Doogie after the teenage genius depicted on TV, by manipulating a single gene. Their work, reported in the September 2 issue of *Nature*, not only sheds light on the molecular underpinings of learning and memory, but could eventually lead to new treatments for age-related dementia.

Image: PRINCETON UNIVERSITY

DOOGIE MOUSE, belonging to a strain made brainier by alterations to a single gene, could remember objects, such as the plastic containers above, for longer than normal mice.

To make precocious rodents, Tsien focused on the gene NR2B, which encodes the NMDA receptor. Because two chemical signals are needed to trigger this nerve cell receptor, it plays a key role in how we form associations. For instance, if you touch a flame, the visual signal and pain signal arrive to the brain at roughly the same time, activating NMDA receptors and creating a memory. Also Tsien's earlier work had shown that limiting the expression of NR2B could impair an animal's ability to learn and remember; mice lacking the gene in certain brain regions were considerably less intelligent.

Demonstrating the reverse--or a positive association between NR2B and cognitive functions--was more difficult. To do so, Tsien first gave his mice extra copies of the gene, and rigged those genes so that their activity would increase as the animals aged. Earlier studies revealed that in young animals from songbirds to primates, NMDA

receptors are activated even by signals that arrive somewhat far apart, facilitating learning. As an animal ages, though, the signals must travel more in step to trip NMDA receptors and cement memories.

Second, Tsien needed to verify that altering the gene indeed affected NMDA receptor activity at the cellular level. For this piece of the puzzle, he turned to Guosong Liu at MIT. Liu devised a novel test for measuring the number and the functioning of NMDA receptors at individual synapses--the gaps between nerve cells--in the brains of the transgenic animals. His results offered good news: mice with extra NR2B copies did have heightened NMDA receptor activity.

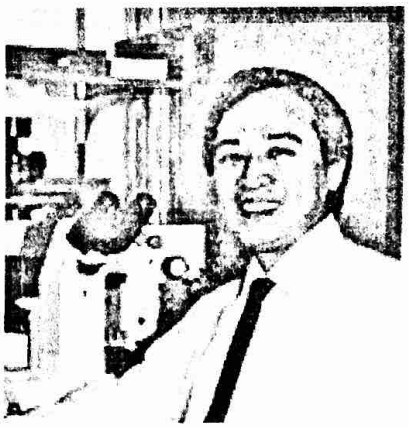

Image: PRINCETON UNIVERSITY

JOE Z. TSIEN has made dumber and smarter than average mice by simply altering a single gene.

The final step was quizzing the little Doogies. In the first test, the researchers put the transgenic mice and normal mice in a space containing two different objects for five minutes. After several days, they replaced one of the objects and brought the mice back in. In this round, the Doogie mice ignored the older object and focused on exploring the new one, whereas the control mice split their time evenly between the two objects, implying that they had not remembered the one they saw before.

In another phase of testing, the animals were placed in a chamber where they received mild shocks. When the mice were returned to the chamber one hour, one day and 10 days later, the Doogie mice consistently showed greater fear than did the normal mice, suggesting that they had stronger emotional memories of the initial experience. To probe another brain circuit, the researchers also taught the animals to be fearful of a certain tone, and again the Doogies had better recall.

Memory aside, the scientists wanted to see whether the transgenic mice actually learned more effectively. To find out, they reconditioned the animals to be frightened by a mild shock or tone in a certain chamber. Then they removed the shocks and sounds and put the mice back into the same chamber. Although the Doogies became more panicky at

first--consistent with the previous testing--they also calmed down sooner and resumed normal behavior. In other words, they were quicker to grasp the change.

One additional experiment, involving a pool of water with a hidden ramp, tested spatial intelligence. If the mice found the ramp, they were able to climb out of the pool. The Doogies learned where the ramp was after three dips, whereas the normal mice required twice as many sessions to master and remember the ramp's location. Says Tsien of the transgenic mice, "they're learning things much better and remembering longer. They're smarter." The mice also stayed sharper later in life. In fact, their brains retained many features common in juevenile brains, including a high degree of plasticity.

The tests confirm that many different brain systems--processing such varied information as sights, sounds and touches--all use a common biochemical pathway, involving NMDA receptors, for learning, an idea first put forth by Donald O. Hebb in 1949. They further prove the often debated theory, called Long Term Potentiation (LTP), that memories arise when two neurons form a lasting connection. Tsien's work "is one of the best pieces of evidence so far" for LTP, says Charles Stevens of the Salk Institute. "[It] is the first study so far to produce a positive effect, and that's why it's so good."

Image: MIT

GUOSONG LIUinvented a novel test for quantifying the number and activity of NMDA receptors at

Perhaps most dramatic, the results show that it is possible to make animals more or less intelligent by tweaking their genes. Humans possess a corresponding gene, although its impact on behavior is as yet unexplored. "It's very exciting and holds the hope of not only making animals smarter, but also, ultimately of having a gene therapy for use in areas such as dementia," says Ira Black of Rutgers University. "This is far in the future and is certainly not something we oculd bring to the bedside tomorrow." But maybe in a decade.