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Scientists Discover Memory-Enhancing Switch

Scientists have genetically engineered mice with enhanced memory that persists until researchers switch it off by removing a drug that controls a gene that encodes a key memory-governing enzyme. With enhanced memory, the mice perform better on memory tests and then revert to normal when the drug is removed.

The achievement, say the researchers who developed the mouse model, offers important insights into the delicate molecular balance by which memory storage is achieved. Although memory-boosting drugs are a long way off, the researchers believe that the work opens new avenues for understanding the molecular basis of memory.

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— **Eric R. Kandel**

Howard Hughes Medical Institute (HHMI) investigator Eric R. Kandel and his colleagues reported their experiments in the March 9, 2001, issue of *Cell*. Lead co-authors of the paper are Gaël Malleret and Isabelle Mansuy, who was formerly in Kandel's Columbia University laboratory. Mansuy is now at the Swiss Federal Institute of Technology in Zürich.

The scientists created the mice by inserting a gene that, when activated by the antibiotic doxycycline, produces an inhibitor of the enzyme calcineurin. In the brain's principal memory-storage region, the hippocampus, calcineurin counteracts the effects of another enzyme, PKA, in signaling pathways governing a process called long-term potentiation (LTP). LTP enhances

connections between neurons and is one of the main neural pathways by which memories are stored in the brain. PKA is a kinase, which adds a phosphate to enzymes, and calcineurin is a phosphatase, which removes a phosphate.

Development of the mouse was prompted by an earlier study conducted at the HHMI laboratories at Columbia University with *Cell* co-authors Danny G. Winder and Isabelle Mansuy, said Kandel. "In that study, we overexpressed calcineurin in mice using this same system by which genes can be switched on and off," said Kandel. "And, we saw that such overexpression inhibited a component of LTP, and interfered with memory storage. We reasoned that inhibiting the action of calcineurin would enhance LTP and memory storage."

After developing the mice, the scientists first performed biochemical studies on slices of hippocampus and electrophysiological studies in whole mice that confirmed that doxycycline enhanced LTP. The whole-animal studies were performed by co-authors Tim V. P. Bliss and Matthew W. Jones of the National Institute for Medical Research in London. "The whole-animal studies allowed recording the effects of calcineurin inhibition for days and convinced us that we were really seeing an enhancement of LTP even in the intact animal," said Kandel.

The researchers next measured the animals' memories in behavioral tests. The researchers found that the calcineurin-inhibited animals were better able to remember when familiar objects were moved to novel locations or replaced with novel objects. The calcineurin-inhibited mice were compared to both normal mice and mice that had been taken off doxycycline.

"An important point is that we built into this experiment tests showing that we could reverse the memory enhancement by switching off the inhibitory gene," said Kandel. "You worry in such experiments that the animals' memory will become better or worse because you've somehow interfered with some normal function during development. But we found that was not the case; and we also did experiments showing that the animals can see, smell and locomote perfectly well, and are well motivated. So we really are seeing an effect on hippocampal learning."

In other studies, the scientists showed that the calcineurin-inhibited animals displayed enhanced spatial memory they were better able remember the location of a platform in a murky water pool. And, the scientists performed tests showing that working memory memory of immediate past circumstances was not affected by the inhibition. In those tests, the animals were required to find food in a radial-arm maze, a task enhanced by immediate recall of the maze arms already explored.

According to Kandel, the mouse studies revealed the importance of a balance of activation and inhibition in memory storage. "One tends to think of memory storage as a process that is only positively directed, involving a mechanism that allows you to store memories," he said. "But our earlier work on lower organisms had revealed inhibitory constraints on memory storage, and in this present work, we demonstrate the first evidence for an inhibitory

threshold in a mammalian brain. It confirms what is really common sense that you only want to store important things in memory, so you need inhibitory constraints that you have to overcome."

Kandel emphasized that further study will likely reveal other balancing mechanisms. He also emphasized that practical applications in the form of memory-enhancing drugs remain possible, yet unclear.

"While it's quite uncertain at this point, these findings could yield a useful target for drugs designed to enhance memory in people with age-related memory loss, although not for those with serious memory loss due to Alzheimer's disease," he said. "Such drugs might prove to be the 'aspirins' of memory in the sense that they are able to enhance memory modestly," he said. Kandel cautioned that any memory-enhancing drugs that target calcineurin would have to be quite specific since calcineurin plays a number of important roles in the body, especially in the immune system.