COMMENTARY

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The recent paper by Tang et al. (1999) describing the genetic enhancement of learning and memory in mice sparked a media frenzy that even a reclusive scientist could not avoid. For a brief period we were saturated by stories from newspapers, television, and radio reporting on these “smart” mice and the “IQ gene” and, inevitably, the possibility of enhancing human intelligence. For those of us in the field of neuroscience, the hypothetical applications of this paper have encountered more skepticism, but the results of the project make a tangible contribution to our current understanding of learning and memory.

The inspiration for the study of Tang et al. comes from the predominant theory on the cellular basis for learning, called Hebb’s rule, which states that synaptic transmission between two neurons will be strengthened if the two cells are simultaneously active and one cell repeatedly excites or causes the other cell to fire (Hebb 1949). This form of synaptic plasticity called long-term potentiation (LTP) clearly exists, as well as the reverse of LTP called long-term depression (LTD), a use-dependent decrease in synaptic strength. However, the relationship of these processes to memory is still in dispute. One implication of Hebb’s rule suggests that improved coincidence detection between neurons will result in improved learning. Tang et al. set out to test this hypothesis. They did this by altering the characteristics of the protein responsible for coincidence detection, the *N*-methyl-D-aspartate (NMDA) receptor. This receptor will only activate when it binds glutamate released by activity in the presynaptic cell and when it senses postsynaptic activity in the form of membrane depolarization. When the NMDA receptor detects these two events within a short time window, it allows calcium into the cell and this calcium is critical for inducing LTP.

The NMDA receptor is composed of an obligatory NR1 subunit and a selection of NR2 subunits (A–D). The NR2 subunit confers different channel properties on the receptor complex. One intriguing subunit difference is the longer excitatory postsynaptic potential (EPSP) observed in NR2B-containing receptors in comparison to NR2A-containing receptors. This longer EPSP suggests that NR2B-containing receptors have a longer time window for detecting pre- and postsynaptic activity resulting in increased coincidence detection and enhanced LTP when activity is less synchronized. The developmental regulation of NR2B supports the relationship between this subunit and increased LTP because the expression of NR2B is highest when the animal is young and decreases in adulthood, correlating well with the higher amount of LTP

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seen in younger animals. Tang et al. seized upon this subunit as an ideal way to enhance coincidence detection and LTP in mice and examine the effects on learning and memory in those animals.

To create the transgenic mice, they overexpressed the NR2B subunit in the forebrain under the control of the CaM kinase II (CaMKII) promoter. Using Northern blots, Western blots, and in situ hybridization they show that NR2B mRNA levels are elevated in areas of the cortex and hippocampus with low expression in other areas of the brain. To confirm that the increased expression had the desired effects on NMDA receptor conductance, they made whole-cell recordings from cultured hippocampal neurons at different time points. They found that the amplitude and duration of glutamate-evoked NMDA currents in the wild-type mouse dropped off sharply by 18 days in culture, but the amplitude and duration of NMDA currents in the transgenic lines remained high at 18 days. These investigators then examined LTP in these mice by doing extracellular field recordings in hippocampal slices from 4- to 6-month-old animals. LTP was substantially increased in the transgenic lines, and a lower frequency stimulus protocol (10 Hz tetanus) that does not induce LTP in control animals did induce LTP in the mutants, indicating improved coincidence detection by the NR2B-overexpressing neurons.

After demonstrating that their animal model did have increased LTP, Tang et al. then tested for changes in learning and memory. They did this with a number of behavioral tests examining several types of learning such as novel-object recognition, associative fear learning, fear extinction, and spatial learning. In these tasks, the transgenic animals clearly performed better than wild-type animals did by both learning faster and retaining memories longer.

One shortcoming of the paper is the lack of data detailing the expression of the *NR2B* transgene. Although the level of the NR2B subunit is shown to be higher in the transgenic animals, the time point(s) at which the data were collected is not specified. A more thorough and detailed examination of the expression of the transgene over time would be useful. The same lack of expression data applies to the electrophysiology in the cultured neurons. The persistence of high-amplitude, long-duration NMDA currents in the transgenic neurons is attributed to higher levels of the NR2B subunit, but the level of NR2B expression in wild-type and transgenic cultured neurons is not compared. It will be important to determine levels of NR2B in these cultured neurons because other laboratories have found that the CaMKII promoter does not express well in cultured neurons (R. Behar and M. Mayford, pers. comm.). Although the increased NMDA current is most likely due to increased NR2B expression, it remains to be proven conclusively.

This paper addresses a central debate in the field of neuroscience: Is LTP a cellular substrate of memory? This topic remains a matter of considerable controversy with strong proponents for either side. The strongest evidence supporting a role for LTP in learning are experiments showing that a block of LTP is correlated with a decrease in learning and memory. Researchers have impaired LTP by both pharmacological agents and numerous gene knockouts and found deficits in two kinds of memory in two brain regions (hippocampal-dependent spatial memory and amygdala-dependent fear conditioning). On the other hand, there are numerous exceptions to this correlation between LTP and memory with knockout mice that show diminished LTP with no deficit in spatial

learning and mice with enhanced LTP but impaired performance in spatial memory tasks (Zamanillo et al. 1999; Migaud et al. 1998).

Although the findings of Tang et al. do not resolve the issue, they support the role of LTP in memory. Previous studies have analyzed assorted knockout mice in which the expected phenotype is impaired synaptic plasticity and behavioral performance. These experiments are questionable (and will always be questioned by critics) because of the possibility of developmental effects resulting in general and nonspecific animal defects. This study began with the specific goal of increasing rather than decreasing the performance of the animal, and the investigators manipulated a gene with a clear and critical role in LTP. Their transgenic mice showed the exact changes in physiology predicted by Hebb's rule with no observable side effects. The mice were then subjected to thorough behavioral testing and showed consistently better performance than their wild-type littermates. This well-designed and executed study makes an important contribution to the body of evidence supporting synaptic plasticity as a cellular mechanism of learning and memory.

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