Generation of a severe memory-deficit mutant mouse by exclusively eliminating the kinase activity of CaMKIIalpha

19 June 2009

A Japanese research group, led by Dr. Yoko Yamagata of the National Institute for Physiological Sciences, has successfully generated a novel kinase-dead mutant mouse of the CaMKIIalpha gene that completely and exclusively lacks its kinase activity. They examined hippocampal synaptic plasticity and behavioral learning of the mouse, and found a severe deficit in both processes. They reported their findings in *Journal of Neuroscience* on June 10, 2009.

Ca2+/calmodulin-dependent protein kinase II alpha (CaMKII alpha) is an enzyme that adds phosphates to a variety of protein substrates to modify their functions. CaMKII alpha is enriched in the hippocampus, the memory center of the brain, and is believed to be an essential mediator of activity-dependent synaptic plasticity and memory functions. However, the causative role of the enzymatic activity of CaMKII alpha in such processes has not been demonstrated yet, because this enzyme has multiple protein functions other than the kinase activity.

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The research group successfully generated a novel CaMKII alpha (K42R) knock-in mouse that completely lacks the kinase activity of CaMKII alpha, and examined the effects on structural, functional, and behavioral expression of synaptic memory. In the K42R brain, tetanus-induced long-term potentiation (LTP), a proposed cellular mechanism of memory, and sustained postsynaptic spine enlargement, a structural basis for LTP, were both impaired, whereas dynamic postsynaptic movement of CaMKII alpha protein was preserved. In addition, the K42R mouse showed a severe deficit in inhibitory avoidance learning, a form of memory dependent on the hippocampus. The research group concluded that the mutant mouse could not form memories and did not remember the events that had just happened.

"We demonstrated that the mutant mouse has a severe memory deficit because of the lack of the kinase activity of CaMKII alpha. This finding supports the idea that the kinase activity of CaMKII alpha is essential to memory functions. Such a memory-deficit mutant mouse could serve as an animal model to study the molecular mechanisms of memory, and be a useful tool for the development and screening of therapeutic reagents for memory-deficit disorders. It may also help open a new therapeutic approach to memory dysfunctions in patients.", said Dr Yamagata.

Source: National Institute for Physiological Sciences