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Multiple Learning Mechanisms in Mouse Eyeblink Conditioning

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Classical conditioning of eyeblink response is a type of associative learning, in which a neutral conditioned stimulus (CS) such as a tone or light is paired with an aversive unconditioned stimulus (US) such as a corneal air-puff or periorbital shock. After several hundreds of repeated presentations of the CS and US, the CS becomes to elicit the conditioned eyeblink response. There are two typical paradigms that differ in the CS-US temporal relationship. In delay paradigm the US is delayed and terminates simultaneously with the CS, while in trace paradigm a stimulus-free trace interval intervenes between the CS and the US. The essential neural circuit in delay paradigm, which resides in the cerebellum and brainstem, has been extensively studied in rabbits. In addition to these essential brain regions, the forebrain including the hippocampus and the medial prefrontal cortex play an important role in trace paradigm. Thus, this learning task has become a good model system that is suitable for analysis of the neural substrates of learning and memory. Although this important basic framework for learning mechanism has been established in rabbits, mice are becoming another important model because of the current progress in gene-manipulating techniques in mice.

We have studied the eyeblink conditioning using several kinds of mutant mice that have some deficits in cerebellar functions. In the course of our study, we found not only the consistent results with those reported in rabbits, but also some exceptions. For example, mice that lack glutamate receptor δ2 subunit (GluRδ2) [1)] or phospholipase Cβ4 subunit [2)] exhibited a severe impairment in delay paradigm, but learned successfully in trace paradigm, even in the '0-trace paradigm', in which the US starts just after termination of the CS. Further analysis showed that ablation of the hippocampus [3)] or systemic administration of NMDA antagonist MK-801 [4)] or mACh antagonist scopolamine [5)] severely impaired learning in GluRδ2$^{-/-}$ mice. These results suggest that contribution of the forebrain to this learning seems to increase in mice that have deficits in their cerebellum. This compensational learning mechanism seems to be similar to the phenomenon that dependency on the forebrain increases when the task demand on the animal is raised, for example in trace paradigm, and cannot be solved by the cerebellum and brainstem alone. I will discuss about the multiple learning mechanisms and its hierarchical control in mouse eyeblink conditioning, along with our recent findings using wild-type mice.

References

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