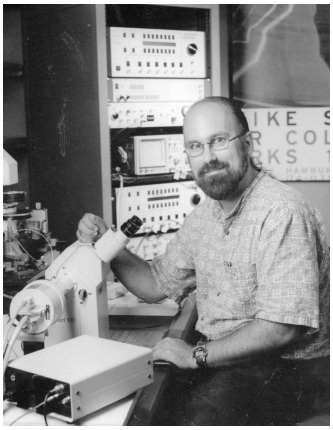

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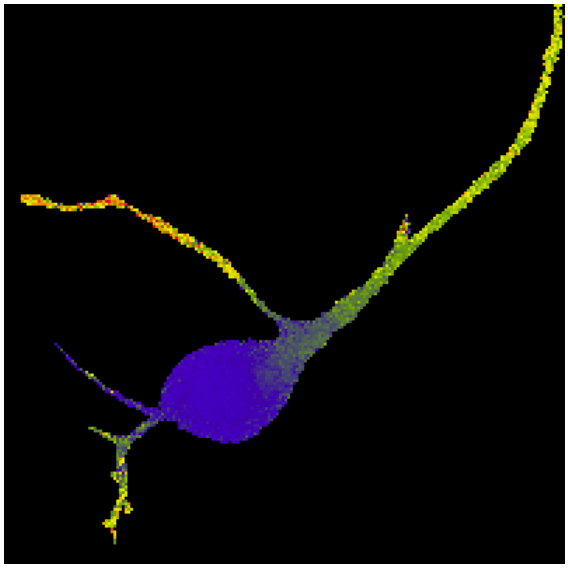

(click on pictures for captions)

Cellular Substrates of Memory

A central hypothesis of modern neurobiology is that memory is stored through use-dependent changes in synaptic strength. Most work in this area has focused upon long-term potentiation and depression (LTP and LTD) of glutamatergic synapses. One limitation of this approach is that the brain regions where LTP and LTD are most often studied, such as the hippocampus, receive information that is so complex that its content cannot be easily characterized. In contrast, in the cerebellum it has been possible to propose a "circuit diagram" for some simple forms of learning such as associative eyeblink conditioning and vestibulo-ocular reflex adaptation. For example, it is possible to assign the conditioned (CS) and unconditioned stimuli (US) in associative eyeblink conditioning to specific pathways (the mossy/parallel fiber system and climbing fibers, respectively). Over the last 20 years, a series of experiments which have used behavioral tasks together with extracellular recording, reversible inactivation and transgenic manipulations have produced a strong case that the cerebellum is critical for these forms of motor learning. In particular, LTD and LTP of the parallel fiber-Purkinje cell synapse have been implicated in acquisition and extinction of eyeblink conditioning, respectively. In recent years, this laboratory has used both electrode and optical recording in cerebellar slice and culture model systems to explore the molecular requirements for induction and expression of these phenomena. In particular, we (and others) have found that induction of LTP in the parallel fiber synapse requires a presynaptic cascade of Ca influx/adenylyl cyclase I/cAMP/PKA and that its expression is also presynaptic. In contrast, induction of LTD at this synapse is triggered by postsynaptic activation of mGluR1 and AMPA receptors together with Ca influx, resulting in

activation of PKC and consequent clathrin-mediated internalization of AMPA receptors. Along the way, we discovered a new form of plasticity, LTD at the climbing fiber-Purkinje cell synapse, which was not anticipated in models of cerebellar learning and which appears to share some induction requirements with parallel fiber LTD. In addition, we have expanded our analysis to include use-dependent synaptic as well as non-synaptic plasticity in the cerebellar output structure, the deep nuclei. At the level of basic science, these investigations are central to an understanding the cellular substrates of information storage in a brain area where the behavioral relevance of the inputs and outputs is unusually well defined. In addition, these investigations have potential clinical relevance not only for cerebellar motor disorders, but also for disorders of learning and memory generally.

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