findings from Fulton et al. (2006) might be the result of the obese phenotype on the activity of the dopaminergic pathway.

Taken together, the data from Hommel et al. (2006) and Fulton et al. (2006) indicate that leptin modulates the activity of mesolimbic dopamine neurons and that, in doing so, leptin may influence both food and drug-related behaviors. However, further investigation is needed to clarify the role of leptin in motivated behaviors other than feeding. For example, a clear link has been found between leptin and the endocannabinoids as reciprocal modulators of hypothalamic circuits underlying motivational aspects of feeding (Jo et al., 2005). Moreover, endocannabinoids positively regulate the mesolimbic dopamine pathway (Cota et al., 2006). Therefore, one hypothesis about the current findings is that leptin may act via changing levels of endocannabinoids to regulate dopamine neurons in the VTA and/or NAc. Future work will need to delineate just how the endocannabinoid system and leptin may interact in these brain areas.

The last decade has seen a vast increase in our understanding of the homeostatic regulators of feeding behavior; however, our ability to translate that into progress on how reward can influence both food intake and body weight has been considerably slower. The current work reflects how these two areas of study with quite different scientific histories are now coming together. The DiLeone group (Hommel et al., 2006) has worked primarily on various aspects of drug taking, but in this study they chose to investigate food intake as the primary endpoint. In contrast, the Flier group (Fulton et al., 2006) has worked primarily on the homeostatic aspects of food intake regulation, but here they chose to study the ability of leptin to alter the effects of a drug of abuse. This illustrates that investigators on both sides of this divide are coming to the conclusion that there are common underlying neuronal processes involved in drug abuse and obesity. Progress on these circuits has the promise to help develop treatment strategies to lower the enormous burden of both of these diseases.

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Multiple Memory Mechanisms in the Cerebellum?

Long-term potentiation (LTP) and long-term depression (LTD) are arguably two of the most widely discussed cellular plasticity mechanisms for learning and memory. However, the extent to which they are required for behavioral plasticity and learning is not clear. In this issue of *Neuron*, Boyden et al. use mice lacking CaMKIV and Hansel et al. use mice lacking αCaMKII to assess the contribution of LTD to cerebellar learning.

The two most widely studied and best understood forms of cerebellar-dependent learning and memory are adaptation of the vestibule-ocular reflex (VOR) and classical conditioning of eyeblink and other discrete responses (Christian and Thompson, 2003; du Lac et al., 1995). The VOR acts to counterbalance the effect of head movement by producing compensatory eye movements in the opposite direction of head movement, which thereby stabilizes images on the retina and prevents blurred vision. Adaptation of the VOR and eyeblink conditioning have somewhat analogous structural bases. In both cases, adaptation in initial cerebellar learning critically involves the cerebellar cortex, while the cerebellar and vestibular nuclei play a more critical role in long-term memory storage (Christian and Thompson, 2005; du Lac et al., 1995; Kleim et al., 2002).

What are the cellular and molecular mechanisms that underlie cerebellar learning? In vitro studies have pointed to a large number of plasticity mechanisms operational within the cerebellar circuits. However, the contribution of these mechanisms to specific forms of behavioral plasticity remains less clear. Ito first proposed cerebellar LTD as the mechanism in the cerebellar flocculus for adaptation of the VOR (Ito, 1982). Cerebellar long-term depression (LTD) is also widely viewed as a possible mechanism of synaptic plasticity of other forms of cerebellar-dependent learning as well (Linden and Connor,

1995). The basic issue addressed by both the Boyden et al. and Hansel et al. studies concerns whether LTD is *the* mechanism underlying adaptation of the VOR (and of a related form of learning called the optokinetic response, OKR) (Boyden et al., 2004; Hansel et al., 2001). Both studies address the issue using knockout mice, Boyden et al. using CaMKIV mice and Hansel et al. using the αCaMKII mice (Boyden et al., 2006; Hansel et al., 2006).

The roles of both αCaMKII and CaMKIV in synaptic plasticity and learning have been well characterized in the hippocampal system. CaMKIV mutant mice can learn hippocampal-dependent contextual fear conditioning normally but are impaired in long-term memory (1 and 7 days) (Wei et al., 2002). Hippocampal LTP in CaMKIV mutants is impaired throughout the 45 min after the tetanus, but hippocampal LTD remains intact in slices from these animals (Ho et al., 2000). Similarly, αCaMKII mutant mice are impaired in the Morris water maze initially, but their performance catches up with the wild-type mice after successive training (Silva et al., 1992b). Consistent with the hippocampus-dependent behavioral impairment, αCaMKII mutants have a hippocampal LTP deficit throughout the 60 min after the tetanus (Silva et al., 1992a).

CaMKIV has also been implicated previously in the maintenance of cerebellar LTD. In the CaMKIV KO mice, cerebellar LTD can be induced, but it is not maintained (Ho et al., 2000). Boyden et al. took advantage of these mice to test the model first proposed by Ito and colleagues that LTD is the mechanism for the adaptive VOR plasticity. CaMKIV is expressed in adult Purkinje cells in the cerebellum in regions implicated in VOR motor learning. Motor learning of the VOR can be induced in the laboratory by specific training protocols involving pairing rotation of the animal's head with changes in the surrounding visual stimuli. Moving the head in the opposite direction as the visual stimulus causes an adaptive increase in the amplitude (gain) of the response, while moving the head and visual stimulus in the same direction causes an adapative decrease in the VOR gain. Previous in vitro results showed that LTD induction is normal in the CaMKIV knockout mice. In line with these prior observations, Boyden et al. found that the initial acquisition for increased or decreased gain of the VOR with high-frequency stimuli is normal in the CaMKIV knockout mice, suggesting that learning in these mice is normal. However, the effects on memory retention at the behavioral level were more complicated than would be predicted by the simple model that LTD is required for VOR learning. While the 24 hr memory for increased gain was impaired, the memory for decreased gain was not impaired. Further, memory for increased gains with low-frequency stimuli was also intact. From these results, the authors argue that although LTD is a likely mechanism for one aspect of VOR plasticity (retention of an adaptive learned response to increased gain), it cannot subserve other aspects. The authors propose that plasticity mechanisms may be used in a task-selective fashion.

A different approach to this same question of whether LTD is the universal plasticity mechanism is to determine to what extent LTD can also serve as a mechanism for other kinds of cerebellar memory. In our lab, we have trained the same CaMKIV KO mice in eyeblink conditioning, and the results are clear. Similar to the results in Boyden et al., we have shown that animals learn the conditioned response normally, comparable to the wild-type controls, but their long-term memory for the learned response is markedly impaired (K. Lee, N.Q. Truong, T.A. Chatila, R.A. Ram, and R.F. Thompson, 2004, Soc. Neurosci., abstract). So LTD can serve as one of the mechanisms for these two quite different forms of cerebellar-dependent memory. Previous studies had also assessed motor learning in animals deficient in LTD induction. As an example, Shibuki et al. (1996) showed that mutants with complete absence of GFAP in glia show no cerebellar cortical LTD and are markedly impaired in eyeblink conditioning. (Incidentally, this is an intriguing example of a critical role glia may play in neuronal plasticity and memory.) In a recent study, Shutoh et al. (2006) analyzed the mechanisms of memory storage of adaptation of the horizontal optokinetic response (OKR), a form of learning analogous to the VOR. They found that the flocculus was essential for initial learning but the long-term trace (1 week) appeared to be established in the medial vestibular nucleus. They also found that both day-long and week-long adaptations were depressed when neural nitric oxide synthase was pharmacologically or genetically disrupted, thus supporting LTD as a mechanism for both short-term and long-term plasticity. It would be interesting to see the effects of blocking neural nitric oxide synthase in the flocculus in the controls and CamKIV knockouts used in the Boyden et al. study.

In a related article, Hansel et al. (Hansel et al., 2006) explore related issues in the CamKII mutant mice. Like CaMKIV, αCaMKII is expressed by Purkinje cells in the cerebellum. Activation of CaMKII by calcium influx has been proposed to be a common requirement for LTP induction at cortical and hippocampal excitatory synapses, but whether CaMKII plays a similar role in cerebellar plasticity has not yet been addressed. Here, Hansel et al. report that cerebellar cortical LTP (i.e., the Purkinje neuron response to repeated parallel fiber stimulation) is normal in the αCaMKII mutant. Conversely, LTD (i.e., the joint activation of parallel and climbing fibers) is decreased in juvenile αCaMKII mutant animals and becomes potentiated in adult αCaMKII. Interestingly, these results would appear to be opposite of what is observed in the hippocampus at the CA3-CA1 synapse, where αCaMKII KO is required for LTP but not LTD. Behaviorally, the αCaMKII KO mutants showed impaired gain-increase adaptation of both the VOR and the OKR. While 24 hr retention of adaptation was not examined, the mutants did show adaptation in the gain-decrease paradigm, although less than wild-type mice. The authors noted that while cerebellar morphology appears grossly normal in the adult animals at the EM light microscopy level, climbing fiber elimination is delayed in the αCaMKII mice. To address whether this delay in climbing fiber elimination could contribute to the decreased LTD seen in the juvenile animals, the authors make use of a selective CaMKII inhibitor, KN-93. Application of KN-93 to wild-type slices from juvenile animals prevented the induction of LTD and in fact actually led to a potentiative response, arguing that αCaMKII plays a direct role in parallel fiber LTD and that the unstable LTD observed in the αCaMKII mice is not due to a secondary effect resulting from the delayed climbing fiber elimination.

Interestingly, Chen et al. (1995) showed that PKC γ KO mice show persistent multiple climbing fiber innervation of Purkinje neurons. These mice display normal LTD but significantly enhanced learning of the conditioned eyeblink response, supporting a general role for climbing fibers as the unconditioned stimulus teaching input in this paradigm.

Both the Boyden et al. and Hansel et al. studies provide support for Ito's LTD hypothesis (Ito, 1982) for adaptation of the VOR, at least for increased gain with higher-frequency stimuli, but argue that other mechanisms of neuronal plasticity must also be involved in other aspects of cerebellar learning (e.g., learning in response to decreased gain and with low-frequency stimulation). As the authors acknowledge in each case, one caveat is that, in both studies, the evidence is basically correlational: the mutants exhibit impaired cerebellar LTD and alterations in adaptation of the VOR (and OKR) in some conditions but not others. With correlations it is always possible that other factors could result in both effects. One such possibility, noted by Boyden et al., is the occurrence of altered patterns of spiking activity important for induction of plasticity at several sites in the circuit (e.g., Smith and Otis, 2003). Boyden et al. obviate this possibility because the original induction of LTD and adaptation of the VOR were normal, only retention was impaired. While the studies of Boyden et al. and Hansel et al. therefore provide us with important insights into the signal transduction mechanisms that are important for cerebellar LTD, further work will be required to firmly establish the causal role of these, and other, factors in various forms of cerebellar plasticity and learning.

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From a Whisper to a Roar: Adaptation to the Mean and Variance of Naturalistic Sounds

In this issue of *Neuron*, Nagel and Doupe make a quantitative assessment of temporal adaptation in the avian auditory forebrain, capturing seemingly complex responses with a simple linear-nonlinear (LN) model of kinetics and gain. A comparison of these findings with similar results in the early visual system shows an important unifying picture of efficient sensory processing and adaptation.

Sensory systems must use neurons that have a limited dynamic range of responses to encode natural stimuli that change over many orders of magnitude. In spite of this potential problem, humans can recognize both speech and the face of the speaker across a wide range of intensities of sound and light. A first guess at a simple neural code might be a linear encoder, where a cell performs a weighted sum of the stimulus over time. Real neurons, however, have a threshold and saturate. As such, when the stimulus intensity varies greatly, a simple weighting over time will cause a cell to exceed its dynamic range, unless the cell does something more complex and nonlinear—in other words, adapt.

How can a neuron encode small variations across large ranges? Quantitative theories of efficient coding recognize that although the overall range of stimulus intensities might be very large, at any given time the range is likely to be much smaller. Thus, one strategy is for a cell to shift its operating range to center on the current mean stimulus value (Figure 1). Even if the mean stimulus remains constant in response to a change in the variation about the mean, or contrast, a neuron can use its dynamic range more efficiently by changing its gain to more closely match the variance of the input distribution (Laughlin, 1981).

A more subtle premise states that given the statistics of natural stimuli, the encoding strategy should change at different levels of signal-to-noise ratio (SNR). Natural sounds (and scenes) are dominated by low temporal frequencies and thus tend to have similar intensity at nearby points in time. Consequently, at low SNR, it is