occur every few hundred milliseconds, and this behavior may determine a useful temporal scale for adaptation. Thus, adapting to single photons in a dim environment, for ~200 ms at the rod bipolar terminal, may represent the tradeoff between adapting locally in time and space while permitting some instability in the adapting signal.

The study by Dunn and Rieke localized the site of adaptation and the general mechanism (synaptic depression), but the cause of the depression remains uncertain. Why exactly is glutamate release depressed for ~200 ms following a previous release event? Other studies examined this synapse in terms of paired-pulse depression, by either simultaneous voltage-clamp recordings from a bipolar cell and a postsynaptic cell or by monitoring bipolar cell exocytosis with capacitance measurements. These studies suggested several possible mechanisms for paired-pulse synaptic depression, including vesicle pool depletion, Ca current inhibition, and negative autofeedback at the bipolar cell terminal (von Gersdorff et al., 1998; Burrone and Lagnado, 2000; Singer and Diamond, 2006). However, several differences exist between the conditions of these previous studies and those for the light-evoked measurements. Further work will be required to make a direct link between the mechanism for synaptic depression at the rod bipolar terminal and the adaptation shown here by Dunn and Rieke (2008).

A further mystery is the purpose of synaptic inhibition in the retina and what roles inhibition plays in visual adaptation. As mentioned above, there are ~30 types of amacrine cells in the retina, most of which are inhibitory and release either GABA or glycine, sometimes directly to the bipolar cell terminal (Wässle, 2004). However, many forms of adaptation seem to persist in the absence of amacrine cell signaling. The synaptic depression in the Dunn and Rieke study is one example. As light level increases, background adaptation in the cone circuitry switches between a mechanism at the cone bipolar cell terminal to a mechanism within the cones themselves, but neither mechanism required synaptic inhibition (Dunn et al., 2007). In addition to adapting to the mean intensity, the retina adapts to contrast or the deviations in light intensity relative to the mean. There are both slow and fast forms of contrast adaptation, but neither of these seems to depend critically on synaptic inhibition (Manookin and Demb, 2006; Beaudoin et al., 2007). Thus, multiple mechanisms for visual adaptation appear to arise from mechanisms at the bipolar cell terminal. How these multiple forms of adaptation could be expressed, in some cases, in the same bipolar cell will be an interesting topic for future study.

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All Asleep—But Inhibition Is Wide Awake

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Depending on the arousal state, neuronal networks display discrete activity patterns that profoundly affect information processing in the brain. In this issue of *Neuron*, Kurotani et al. report bidirectional modification of inhibition by oscillatory patterns in the neocortex; a mechanism likely to control the impact of these neurons in a state-dependent fashion.

Why is waking up, especially early in the morning and prompted by an alarm clock, often so difficult? One reason maybe that the transition from sleep to wakefulness requires drastic changes in the modus operandi of our brain. During slow-wave sleep (or deep sleep), network activity in the neocortex is characterized by slow, large-amplitude oscillations. The

intracellular correlate of this network activity are up and down states, which represent periods of depolarized and hyperpolarized membrane potential occurring at frequencies of less than 1 Hz. In contrast, transitions to both rapid-eye movement sleep and to the alert state abolish down states, leaving neocortical neurons in a depolarized, tonically activated mode (Steriade et al., 2001).

Slow-wave sleep has for a long time been implicated in memory consolidation (e.g., Wilson and McNaughton, 1994), but the underlying cellular mechanisms are only just beginning to emerge (see below; Hoffman et al., 2007). This question is technically difficult to address since in vivo experiments rarely permit a detailed analysis of signal processing at the cellular level, let alone pharmacological intervention. The study by Kurotani and colleagues (2008) in this issue of *Neuron* has circumvented these problems by mimicking firing patterns typical for slow-wave sleep and arousal in neocortical layer 5 pyramidal neurons recorded in acute brain slices (for a different approach, see Sanchez-Vives and McCormick, 2000). This approach revealed a striking, bidirectional modification of somatic inhibition in these neurons: long-lasting depression was induced by repetitive firing from depolarized membrane potentials as well as by 5 Hz oscillations. In contrast, slower oscillations (0.5 Hz) or firing from a hyperpolarized state caused long-lasting potentiation of somatic inhibition. Synaptic stimulation was switched off during the induction of plasticity, indicating that association of pre- and postsynaptic activity is not required. Rather, the modifications appear to affect somatic inhibition in a global manner. Consistent with this, both induction and expression were found to be postsynaptic.

How can comparatively subtle variations in neuronal firing patterns, which do not even change the average firing frequency, have such different effects on inhibition? The answer lies in the activation and inactivation properties of voltage-gated Ca^{2+} channels. R-type Ca^{2+} channels are inactivated at rest and require hyperpolarization for recovery from inactivation. Thus, Ca^{2+} influx through this source only occurs during firing patterns incorporating hyperpolarized episodes, which potentiates somatic inhibition via exocytosis of $GABA_A$ receptors. This effect is dynamically balanced by activation of L-type Ca^{2+} channels resulting in $GABA_A$ receptor endocytosis and depression of somatic inhibition. As a result, the relative activation levels of the two types of Ca^{2+} channels determine the direction of synaptic modification. This regulation is likely to occur in response to physiologically relevant states in vivo, as slices prepared from rats that had been in slow-wave sleep prior to sacrifice displayed stronger somatic inhibition than those obtained from awake animals.

A functionally analogous observation has been made in hippocampal neurons, where prolonged high-frequency firing causes global depression of inhibitory synaptic transmission, albeit by a different mechanism involving a shift in the reversal potential of GABAergic currents (Fiumelli et al., 2005). In contrast, the bidirectional changes in inhibition observed by Kurotani et al. (2008) were not associated with a change in the GABAergic reversal potential. A shift in the reversal potential of GABAergic events may have been missed in the study by Kurotani et al. (2008) due to the use of whole-cell recording, whereas the study by Fiumelli and colleagues (2005) employed perforated-patch recording so as to maintain the intracellular chloride concentration. Together, these data suggest that activity-dependent changes in inhibition may be mediated by distinct but functionally similar, and indeed potentially additive, mechanisms in cortical neurons. It is worth noting that, on the face of it, the modifications described by Kurotani et al. (2008) constitute a positive feedback loop, since more depolarized neurons will receive less inhibition further increasing the level of depolarization. To prevent runaway excitation additional compensatory mechanisms to upregulate inhibition will have to be in place. Potential candidates include frequency-dependent and associative LTP of inhibitory synaptic transmission (reviewed in Gaiarsa et al., 2002).

The new findings of Kurotani et al. (2008) suggest that the axo-somatic domain of pyramidal neurons will be less excitable during slow-wave sleep compared to the awake state. In this situation, excitatory synaptic input on the dendritic tree may more readily undergo activity-dependent modifications independent of axonal action potential output; a mechanism which has been proposed for memory consolidation during sleep (Sejnowski and Destexhe, 2000). Recent evidence also suggests that long-range connectivity between cortical areas is markedly reduced in sleeping subjects, an observation which could underlie the loss of consciousness during sleep (Massimini et al., 2005). Since layer 5 pyramidal neurons constitute a major output pathway of neocortical columns, increased somatic inhibition could, in part, account for this apparent breakdown of connectivity. In contrast, recent studies show that recurrent synaptic transmission between layer 5 pyramidal neurons is enhanced during up states (Kole et al., 2007; Shu et al., 2006). Thus, in a background of reduced axo-somatic excitability, local recurrent excitation within the same cortical column appears to be selectively enhanced, in line with the hypothesis that up states are generated by intracortical recurrent transmission (reviewed in Hoffman et al., 2007).

Analysis of the cellular mechanisms underlying cortical oscillations will teach us a lot about the function of the neocortex. The new findings of Kurotani et al. (2008) show that changes in the strength of inhibition are likely to have a profound impact on cortical network activity during different arousal states. Future experiments will be required to investigate the importance of these changes in inhibition for network activity in vivo. Of note, several anesthetics induce activity states very similar to slow-wave sleep, making it possible to test hypotheses derived from in vitro experiments in the intact system.

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Tasteless Food Reward

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Food palatability acts on the dopaminergic reward system to override homeostatic control; however, whether postingestive calorie load in the absence of taste affects this system remains unclear. In this issue of *Neuron*, de Araujo et al. show that mice lacking functional "sweet" taste receptors (*trpm5*$^{-/-}$) develop a preference for sucrose by activating the mesolimbic dopamine-accumbal pathway, solely based on calorie load.

There is no question that the current obesity epidemic has galvanized the scientific community to feverishly investigate the neurobiological mechanisms controlling food intake. It is incontrovertible that the hypothalamus regulates the homeostatic control of food intake by receiving, coordinating, and responding to peripheral metabolic cues. The importance of the hypothalamus in body weight regulation is underscored by conditionally knocking out AgRP neurons in the arcuate nucleus in adulthood (Gropp et al., 2005; Luquet et al., 2005), as these mice will starve to death if left unattended. By integrating these metabolic signals, the hypothalamus regulates food intake and energy expenditure to a body weight "set point." However, it is also clear that, in addition to the homeostatic regulation of food intake, there is substantial influence from higher brain centers (Berthoud, 2007).

The mesolimbic dopamine reward system is one such higher brain center that is important in neurobiological control of food intake (Palmiter, 2007). This is clearly demonstrated in dopamine-deficient mice, as they are hypoactive and hypophagic and die of starvation within 3 weeks of age (Szczypka et al., 1999). Activation of mesolimbic dopamine neurons in the ventral tegmental area (VTA) leads to dopamine outflow from the nucleus accumbens (NAc). This mesolimbic dopamine-accumbal projection is critical to reward-related behavior and has been well studied in models of drug addiction (Kalivas and Volkow, 2005). Food palatability and hedonic value are critical to the overall regulation of food intake and significantly contribute to obesity by overriding long-term homeostatic control in today's highly palatable, energy-rich food environment. Highly palatable foods increase dopamine concentrations in the NAc (Hernandez and Hoebel, 1988), and the hedonic value of sucrose can be attenuated by dopamine antagonists (Bailey et al., 1986). The mesolimbic dopamine-accumbal pathway is also targeted by peripheral metabolic hormones that control food intake, including ghrelin (Abizaid et al., 2006) and leptin (Hommel et al., 2006), which indicates that there is significant crosstalk between metabolic hormones regulating homeostatic and reward-based food intake.

Recent evidence suggests that neurons in the hypothalamus can sense and respond to the changes in metabolic value of ingested nutrients. However, it remained to be determined whether the mesolimbic dopamine system, critical for reinforcing food palatability and hedonic value, could also sense metabolic value of ingested nutrients independent of taste. The study by de Araujo et al. (2008), published in the current issue of *Neuron*, investigated this question by cleverly and logically designing a series of behavioral, neurochemical, and electrophysiological experiments in mice that lacked a functional transient receptor potential channel M5 (TRPM5, designated "KO") (Zhang et al., 2003). The TRPM5 ion channel is highly expressed in taste receptor cells (Perez et al., 2002) and is essential for sweet taste signaling (Zhang et al., 2003). This study represents a major step forward in reward-related food intake behavior, as it shows that brain dopamine reward circuits can be controlled by calorie load, independent of food palatability, hedonic value, or functional taste transduction.

In the first set of behavioral experiments, the authors set out to show that KO mice were acutely insensitive to the orosensory or "sweet" rewarding properties of sucrose. As expected, water-deprived WT mice were more strongly attracted to sucrose solutions compared to water (as measured by number of licks for the sucrose solution/number of licks for water), whereas KO mice exhibited no preference for sucrose over water. Additional preference tests confirmed that the KO mice were insensitive to the orosensory "sweet" rewarding properties of sucrose. These sweet-insensitive mice