ing cascades and their cytoskeletal dependence. Such plasticity in cell signaling after tissue injury may represent a key, unique mechanism in converting acute to chronic pain. Activation of sensory neurons during acute bouts of pain following injury may slowly lead to transcriptional and posttranslational changes modifying the composition of the cytoskeleton and its signaling interactions, such as with prostaglandin receptors as shown in the "primed" state in Figure 1. An alternate model that should be considered includes the possibility that hyperalgesic priming induces a change in cytoskeleton-based active transport processes, and that this change leads to the increased transport of components of the signaling pathway involving PKA, PKCϵ, and ERK1/2 signaling to the compartment where EP receptors mediate their effects. In this model, there would be a requirement for constant active transport of signaling molecules necessary for epinephrine-induced sensitization and for EP receptor-mediated sensitization in the primed state. Future studies will certainly endeavor to determine the basis for this dependence on cytoskeletal integrity. These modifications in cytoskeletal signaling may amplify nociceptive sensory neuron activity leading to chronic pain even in the absence of significant tissue injury or inflammation. Thus, a possible therapeutic modality for chronic pain may attempt to maintain cytoskeletal signaling in a "quiescent" rather than a "primed" state.

While basic science theory rarely finds its way to the bedside immediately, the results of Dina and colleagues may already elaborate on the pathophysiologic basis of a current medical therapy. Gout is a condition resulting from the deposition of urate crystals in joints, leading to a painful, inflammatory arthritis, and is the most common cause of inflammatory arthritis in men over the age of 40. Colchicine, a microtubule inhibitor, is the oldest treatment of acute gout. The traditional view is that colchicine inhibits microtubule-based inflammatory cell chemotaxis, phagocytosis, and generation of leukotrienes (Emmerson, 1996). However, the work of Dina et al. (2003) suggests that colchicine may also work directly at the level of sensory neurons, reducing their response to inflammatory mediators in joints. Interestingly, in a controlled study of colchicine in gout, pain scores fell before clinical scores related to joint inflammation after colchicine treatment (Ahern et al., 1987). Thus, colchicine may produce analgesic effects independent of inflammation. Recent success of colchicine in a clinical trial with osteoarthritis, a predominantly noninflammatory condition, also supports this notion (Das et al., 2002). The hypothesis that colchicine modulates sensory neuron function in arthritic conditions is exciting and should drive future research into the neuronal cytoskeleton as a possible therapeutic target for acute and chronic pain.

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A Form of Presynaptic Coincidence Detection

In this issue of *Neuron*, Sjöström et al. provide evidence for a novel presynaptic mechanism for coincidence detection in induction of timing-dependent LTD. In their scheme, simultaneous activation of presynaptic NMDA receptors and CB1 endocannabinoid receptors induces a long-lasting reduction in presynaptic transmitter release.

In spike timing-dependent synaptic plasticity (STDP), the direction and magnitude of synaptic modification depends critically on the relative timing of the pre- and postsynaptic spikes. This form of Hebbian plasticity was first demonstrated in vitro (Bi and Poo, 2001), and its functional consequences have been explored both theoretically (Abbott and Nelson, 2000) and experimentally (Allen et al., 2003; Fu et al., 2002). A standard description of STDP is an asymmetric window representing synaptic modification as a function of the pre-/postsynaptic interspike interval (Bi and Poo, 2001). While the basic asymmetry is preserved across a wide range of glutamatergic synapses, the width of the window varies considerably (e.g., compare Froemke and Dan, 2002, with Debanne et al., 1998), which may be important for neural computation (Abbott and Nelson, 2000). Thus, knowing what cellular processes determine the temporal window is of great interest not only from a mechanistic point of view but also at the functional level. To determine the

sign and magnitude of synaptic modification, there must be certain cellular machinery that compares the timing of pre- and postsynaptic spikes with millisecond precision. What serves as the coincidence detector? Up to now the best candidate molecule for performing coincidence detection has been the postsynaptic NMDA receptor, the gating of which requires not only the binding of glutamate secreted by the presynaptic neuron but also a postsynaptic depolarization that removes the Mg^{2+} block (Malenka and Nicoll, 1999). This new study by Sjöström et al., however, suggests the involvement of a presynaptic mechanism for coincidence detection in LTD induction.

In a previous report, Sjöström et al. have demonstrated robust STDP in layer 5 pyramidal neurons in the rat visual cortex (Sjöström et al., 2001). In the present study, they focused on the cellular mechanisms underlying the induction of spike timing-dependent LTD (tLTD). As a first step, they asked whether tLTD is expressed pre- or postsynaptically. Using a traditional set of criteria for presynaptic expression of synaptic modification (CV analysis and short-term depression), they showed that tLTD is best accounted for by a reduction in presynaptic release of glutamate. This result fits well with a previous finding, in which LTP in cortical layer 5 is accompanied by an increase in short-term depression, indicating presynaptic expression (Markram and Tsodyks, 1996).

If the expression of tLTD is presynaptic but the induction depends on postsynaptic spiking, some sort of retrograde signal must be present. In studying the mechanisms of synaptic plasticity, there has been a long history of hunting for retrograde messengers, with quite a few molecules on the candidate list: nitric oxide, carbon monoxide, arachidonic acid, neurotrophins, etc. (Malenka and Nicoll, 1999). Newly added to the list are the endocannabinoids, which have been recently implicated in the induction of several forms of short- and long-term synaptic plasticity (Kreitzer and Regehr, 2002). Sjöström et al. thus examined the role of presynaptic CB1 receptors in the induction of tLTD. Two experiments strongly indicated the involvement of cannabinoid signaling. First, an antagonist of CB1 receptors blocked the induction of tLTD, indicating that the receptor is necessary. Second, direct application of CB1 receptor agonists paired with high-frequency presynaptic spiking led to significant LTD in the absence of postsynaptic spiking, and this effect persisted in the presence of postsynaptic BAPTA, a fast Ca^{2+} chelator that completely blocks tLTD. This result suggests that cannabinoids released from the postsynaptic cell are also sufficient for the induction of LTD. Such LTD induced by CB1 receptor agonists (cLTD) is similar to tLTD in its presynaptic expression, and cLTD and tLTD occluded each other, suggesting that they are mediated by the same mechanism.

If the role of the postsynaptic cell is to release a retrograde messenger, what is the role of the presynaptic neuron in LTD induction? Sjöström et al. showed that presynaptic spiking is required not only for tLTD but also for cLTD, suggesting that a presynaptic event other than the activation of CB1 receptors is also required for LTD induction. The involvement of presynaptic metabotropic glutamate receptors (mGluRs) in certain forms of LTD led them to investigate the role of various glutamate receptors in tLTD/cLTD. Surprisingly, NMDA receptors, rather than mGluRs, appeared to be required for cLTD. Given that cLTD is expressed presynaptically and does not require postsynaptic spiking, they concluded that the effect requires activation of pre- rather than postsynaptic NMDA receptors. Together, these results suggest that tLTD is expressed presynaptically, and its induction requires simultaneous activation of presynaptic NMDA autoreceptors and CB1 receptors.

This work immediately raises several intriguing questions. First, how is LTD induced by low-frequency spike pairing? Sjöström et al. demonstrated that while cLTD can be induced only with high-frequency presynaptic firing, tLTD induction is independent of spike frequency. Is there another retrograde messenger responsible for low-frequency tLTD, as the authors suggested? Second, what cellular processes determine the width of the LTD window, and what underlies its diversity among different synapses? The authors suggested that the time course for the availability of endocannabinoids sets the temporal specificity, since blocking the degradation of endocannabinoids can prolong the LTD window. However, in principle the temporal window can be affected by the entire cascade of cellular events leading to LTD, and artificially prolonging any step (e.g., the duration of increases in intracellular Ca^{2+}) may increase the width of the window. Future experiments are needed to identify which factors determine the temporal specificity of tLTD under physiological conditions. Finally, how general is the mechanism proposed here? Many previous studies have indicated that the expression of LTD is accompanied by dephosphorylation and internalization of AMPA receptors (Malenka and Nicoll, 1999). It is important to understand the relationship between these pre- and postsynaptic forms of LTD expression.

In summary, this intriguing new study by Sjöström et al. suggests a novel presynaptic coincidence detection mechanism for LTD induction, complementing the well-established postsynaptic mechanism for LTP induction. While presynaptic coincidence detection has been previously demonstrated (Carew et al., 1984), the work of Sjöström et al. provides a nice addition to the rich repertoire of mechanisms for long-term synaptic plasticity.

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Dissociating Intensity from Valence as Sensory Inputs to Emotion

In this issue of *Neuron*, Small and colleagues used fMRI to find evidence for a neural segregation of two dimensions underlying human gustatory experience: intensity and valence. These results join several recent reports that challenge long-held notions regarding amygdaloid representation of negatively valenced events.

A salad of perfectly grilled woodsy-flavored calamari paired with subtly bitter pale green leaves of curly endive and succulent petals of tomato flesh in a deep, rich balsamic dressing. Delicate slices of pan-roasted duck breast saturated with an assertive, tart-sweet tamarind-infused marinade. A big, vibrant Pinot Noir with ripe, sun-dried cherry fruit and smoky, wood-spiced notes. Hungry? The above descriptions serve to illustrate how the subjective complexity and infinite variety of gustatory experience may rest upon only a few primary dimensions such as quality (e.g., sweet, bitter, sour), intensity (subtle or robust), and hedonic tone or valence (pleasant or unpleasant). Such a coarse coding scheme may be likened to the retinal decomposition into short, medium, and long wavelengths underlying the experience of color, but in fact, it deviates in a critical regard. Unlike vision, reward value appears to be a fundamental dimension of gustatory sensation, without need for higher-order stimulus associations. This characteristic may infuse chemosensory experience with an acute emotional primacy (Schiffman, 1974).

In humans' present ecological niche, many eat for pleasure. The origins of taste preference, however, are utilitarian, not esthetic. For example, sweetness is common to safely edible foods, whereas bitterness may signify poison or spoilage. Therefore, humans do not enter the world with a tabula rasa palate, as evidenced by aversive responses to bitter taste in neonates (Steiner et al., 2001). That said, food preference is also dynamic and follows a developmental course that is modulated by the powerful influence of culture (Rozin and Fallon, 1987). For example, although highly aversive to adults, for young children excrement is not excluded from the list of appropriate things to place in one's mouth (despite other neonatal taste aversions). Less appallingly, the appropriateness of foods for different times of day and restrictions for their complimentariness have a developmental time course as well. For instance, the idea of ketchup-drizzled ice cream delicately perched on top of a succulently juicy hot dog may seem a quite sensible breakfast during childhood.

Recent work has significantly advanced understanding of neural building blocks underlying hedonics of chemosensory experience (Zald et al., 1998; Gottfried et al., 2002; Anderson et al., 2003; Small et al., 2003 [this issue of *Neuron*]). In this issue of *Neuron*, Small and colleagues used fMRI to examine the neural basis of why things taste good or bad and how the neural coding of these hedonic dimensions is related to the intensity of taste. Low and high concentrations of sucrose and quinine sulfate were administered such that the subjective intensity and hedonic quality could be examined independently. These two dimensions are normally strongly positively correlated in everyday life. For example, the bitterness of vinegar may be pleasing at low concentrations, but strongly aversive at high concentrations. Through careful manipulation, Small et al. found that the often-correlated dimensions of valence and intensity are supported by dissociable neural substrates. In particular, responses in the pons, mid-insular cortex, and the amygdala responded commensurately with the intensity of taste irrespective of its hedonic quality. In contrast, the anteroventral insular cortex and secondary taste areas in orbitofrontal cortex, inter alia, were responsive to hedonic value irrespective of intensity. Furthermore, the right caudolateral orbitofrontal cortex was more responsive to the pleasant experience of sucrose, and the anterior left orbitofrontal cortex and dorsal insular cortex were more responsive to the unpleasant experience of quinine.

The results of Small's study of taste bear remarkable similarity to our recent results in olfaction (Anderson et al., 2003). In a similar design, we found that the amygdala and adjacent primary olfactory cortex were driven by the intensity of odorants independent of their judged valence, and conversely, distinct right and left orbitofrontal regions responded to pleasant and unpleasant valence, independent of judged intensity. The striking convergence of these two studies provides firm ground for two notions regarding the neural representation of affective responses.

First, electrophysiological, lesion, and imaging studies have in the past pointed to an essential role of the amygdala in the processing of threatening, fearful, and highly aversive events (Aggleton, 2000). This view has been challenged by findings demonstrating amygdala involvement in processing positively valenced events (Cahill and McGaugh, 1990). Such indeterminacy of what characterizes amygdala responsiveness is likely related to the multidimensional nature of affective space. Intensity and valence are often asymmetrically correlated between valences. Viewing negative stimuli (e.g., a picture of a vicious dog) typically results in a more intense and arousing subjective and physiological response than viewing positive stimuli (e.g., a puppy). The Small study demonstrated that when this inequity in experiential intensity is eliminated, the amygdala responds robustly and equally both to events evoking positive and to events evoking negative hedonic experience. Such a pattern of response could reflect that the amygdala codes the intensity of experience irrespective of valence, or rather, that it codes variations in both pleasant