that dendritic spikes leave a synaptic plasticity trace, even following a single trial (Remy and Spruston, 2007), and also trigger long-term changes of intrinsic excitability that favor further dendritic spike generation by the same input pattern (Losonczy et al., 2008). First, this makes the "win" of the activated inputs a more emphatic and durable one: not only have they succeeded in triggering a local spike that will potentiate their strength, but they also reduce the chances of other inputs being potentiated, providing the winning inputs with a long-term advantage. Second, reducing the overall frequency of potentiation-triggering events (particularly if the failure of subsequent events to trigger dendritic spikes might be linked to long-term depression) might be a good way of implementing dendritic gain control and ultimately homeostasis of synaptic strength, both locally and globally. Also, as noted by the authors, this mechanism sets a limit on the number of input patterns that can be stored with dendritic spikes, as well as how frequently those patterns can be retrieved, to a maximum of ~1 pattern per second. Thus, placing dendritic spikes in context shows that they depend crucially on the history of activity, and decisively shape the future of synaptic integration in the same neuron, over both short and long timescales. This sharpened focus on competition between different cooperative groups of synaptic inputs that drive dendritic spikes also allows one to speculate that Gore Vidal's characteristically tart and cynical observation about human endeavor may also apply to synaptic integration.

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Nipping Fear in the Bud: Inhibitory Control in the Amygdala

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Cortical and thalamic inputs to the lateral amygdala are recruited during auditory fear conditioning. In this issue of *Neuron*, Pan et al. describe a new mechanism of GABA-mediated modulation at these synapses, involving target-specific suppression of glutamate release through differential activation of GABAb receptors on glutamatergic inputs to neurons and interneurons.

The amygdala is a subcortical brain structure, consisting of several interconnected nuclei (Pitkanen et al., 1997), which is critically involved in fear-related behavioral responses both in humans and animals (Fanselow and LeDoux, 1999; Davis and Whalen, 2001; Maren and Quirk, 2004). Given that interneurons in the amygdala, specifically in its lateral nucleus (LA), receive massive excitatory inputs (Smith et al., 1998), they are well positioned to control the firing rate of principal neurons by releasing the inhibitory neurotransmitter GABA on them. The latter is also promoted by the intrinsic membrane properties of interneurons in the LA allowing these cells to maintain high-frequency spiking in response to postsynaptic depolarization without a significant frequency accommodation (Mahanty and Sah, 1998). The inhibitory neurotransmitter γ-aminobutyric acid (GABA), released by local circuit interneurons, mediates inhibition in different regions of the brain, including the amygdala, through its binding to either ionotropic $GABA_A$ or G protein-coupled GABAb receptors. While activation of

$GABA_A$ receptors results in fast, chloride-current-mediated inhibitory responses in postsynaptic neuronal membrane, GABAb receptor activation leads to the slowly developing postsynaptic hyperpolarization associated with the opening of potassium channels. GABAb receptors are also often expressed on glutamatergic nerve terminals where their activation by GABA, spilling over from neighboring GABAergic synapses, suppresses release of excitatory neurotransmitter glutamate by diminishing intraterminal Ca^{2+} influx. The interaction between excitatory (glutamatergic) inputs, which could be controlled heterosynaptically through activation of GABAb receptors on glutamatergic terminals, and time-locked inhibitory postsynaptic responses, both $GABA_A$ and GABAb receptor-mediated, defines the spiking output in the activated neuronal network. This might be, eventually, reflected at the behavioral level. The prevalence of inhibition, as demonstrated with electrophysiological recordings both in slices and behaving animals, explains a notoriously low firing rate of projection neurons in the LA (Repa et al., 2001), as opposed to frequently firing interneurons. Nevertheless, the mechanisms of GABAergic modulation of the neuronal network functions in the amygdala are far from being completely understood. The exciting new study by Pan et al. (2009) in this issue of *Neuron* sheds light on a new regulatory mechanism in the LA, implicating target-specific modulation of excitatory neurotransmission in afferent projections to the LA through activation of GABAb receptors on glutamatergic terminals.

Presynaptic GABAb receptors could be found on glutamatergic nerve terminals forming synapses on both principal neurons and local circuit interneurons. Activation of these receptors with the exogenously applied selective agonist was shown previously to result in nearly identical decreases in glutamate release in inputs to neurons or interneurons (e.g., Porter and Nieves, 2004). In the present study, the authors provide evidence that GABA, endogenously released in response to short trains of presynaptic stimulation (priming) of either cortical or thalamic inputs to the LA (Shin et al., 2006), suppressed glutamatergic neurotransmission in unstimulated heterosynaptic inputs to neurons (thalamic or cortical inputs, respectively) at very short time intervals after the train, while inputs to interneurons remained unchanged. The cortical and thalamic inputs to the LA (originating in the auditory cortex and auditory thalamus, respectively) are implicated in auditory fear conditioning, when the experimental subject learns to fear the sound. The experiments were performed on genetically modified mice, selectively expressing green fluorescent protein (GFP) in their inhibitory cells. Therefore, interneurons could be readily identified in brain slices and targeted for electrophysiological recordings. The decrease in synaptic efficacy at inputs to projection neurons was due to activation of GABAb receptors on corresponding glutamatergic nerve terminals, as it was not observed when presynaptic GABAb receptors were pharmacologically blocked. The priming of thalamic input was not associated with any detectable changes in the amplitude of presumable single-quantum synaptic responses, evoked by "minimal stimulation," in the cortico-amygdala pathway. However, the frequency of failures of synaptic transmission in response to minimal stimulation was increased, indicating that the neuron-specific suppression of glutamatergic neurotransmission was due to the decreased probability of glutamate release. Consistent with the requirement for GABA pooling in the vicinity of glutamatergic terminals forming synapses on neurons for the inhibition to occur, the magnitude of heterosynaptic suppression of synaptic strength in cortical input to the LA positively correlated with the frequency and intensity of presynaptic stimulation and depended on the efficiency of GABA reuptake. This complements a previous finding indicating that simultaneous activation of several interneurons, leading to the significant pooling of GABA, might be needed for activation of GABAb receptors (Scanziani, 2000).

What is the mechanism for selective suppression of excitatory inputs to principal neurons (as opposed to interneurons)? Combining electron microscopy with the pre-embedding immunogold method, the authors demonstrated that the target specificity of presynaptic inhibition was not due to the lack of GABAb receptors on glutamatergic terminals forming synaptic contacts with interneurons, as functional GABAb receptors were found on afferent terminals synapsing on both neuronal cell types. The authors hypothesized that the observed selectivity of presynaptic inhibition could be mediated by differential accumulation of synaptically released GABA in the vicinity of principal neurons or interneurons. They used an outside-out membrane patch, pulled from a principal neuron, as a detector of GABA released in response to activation of afferent projections. The experiments with the "sniffer-patch" technique demonstrated that more GABA was accumulated in the proximity to the soma of principal neurons than interneurons following a short train of high-frequency presynaptic stimulation. Moreover, the size of GABAb receptor-mediated postsynaptic responses, evoked by high-frequency stimulation trains, was significantly larger in principal neurons than in interneurons. Because GABAb receptors are most commonly expressed in dendrites, the latter finding supports the notion that more GABA could be accumulating near neuronal dendrites. The analysis of evoked fast inhibitory postsynaptic responses has revealed that the strength of direct GABAergic inhibitory inputs was greater in neurons, while spontaneous single-quantum inhibitory postsynaptic currents had similar amplitudes in neurons and interneurons. Thus, in principle, a denser GABAergic innervation of neurons, as opposed to interneurons, could explain the apparently higher levels of accumulated GABA in the proximity to neuronal glutamatergic terminals compared to terminals synapsing on interneurons (Figure 1). Consistent with such an explanation, it has been previously demonstrated that the majority of inhibitory GABAergic terminals in the basolateral amygdala form synapses on the somata or proximal dendrites of principal neurons, with fewer terminals contacting more distal dendritic branches (Smith et al., 1998). On the other hand, only a small fraction (~6%) of all synaptic inputs to interneurons in the BLA was shown to be GABAergic, while glutamatergic fibers accounted for the majority of synaptic contacts made on these inhibitory cells.

Conversely, possible differences in the mechanisms of GABA release could, at least in part, explain the target specific pooling of GABA associated with the high-frequency presynaptic activity. If multiquantal release occurs at inhibitory inputs to principal cells, it would lead to

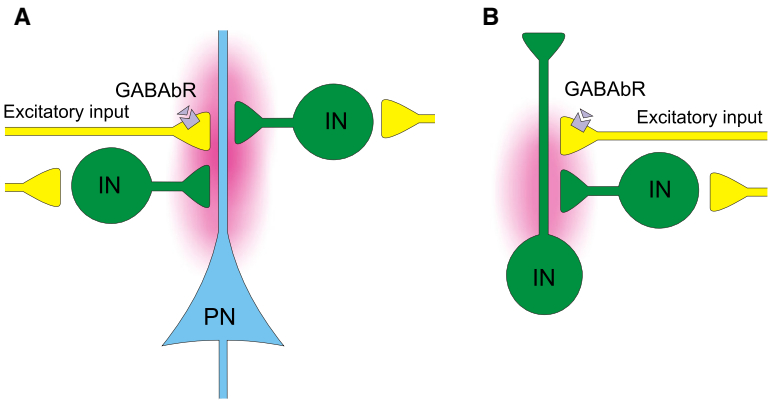

Figure 1. Differential Modulation of Glutamate Release in Afferent Projections to LA Principal Neurons and Interneurons through Activation of Presynaptic GABAb Receptors
Denser GABAergic innervation of neurons (A) rather than interneurons (B) could result in a greater accumulation of GABA (shown as a pink cloud), spilling over from GABAergic synapses, in the vicinity of glutamatergic terminals forming synapses on neurons (A). This could lead to the more significant suppression of neurotransmission at excitatory inputs to principal neurons. IN, interneuron; PN, principal neuron; GABAbR, GABAb receptor.

the enhanced GABA accumulation, even if the numbers of GABAergic fibers innervating the cell are similar for neurons and interneurons. The existence of multiquantal GABA release from single release sites has been previously demonstrated at GABAergic synapses in the cerebellum (Auger et al., 1998). Therefore, it might be interesting to compare the number of quanta released at individual sites of synaptic transmission in GABAergic inputs between principal neurons and interneurons. Another testable possibility is that neurons and interneurons could receive inputs from spatially segregated groups of interneurons. Under this scenario, differences in intrinsic membrane excitability and/or release properties of groups of interneurons, innervating neurons or interneurons, respectively, could lead to the cell-type-specific differences in inhibitory inputs. Moreover, GABAb receptors are heterodimers consisting of GABAb1 and GABAb2 subunits. There are two isoforms of GABAb1 subunit: GABAb1a and GABAb1b. It has been recently demonstrated that the existence of two different GABAb1 subunit isoforms is functionally relevant, as they could differentially contribute to specific neuronal functions and behavioral responses (Jacobson et al., 2006). It remains to be determined whether the differences in GABAb receptor-mediated suppression of glutamate release between inputs to neurons and interneurons might be related to molecular diversity in the GABAb receptor subunit composition (specifically, diversity in GABAb1 subunit, as in Vigot et al., 2006).

What could be the functional significance of the newly discovered modulatory mechanism? During fear conditioning, the same neurons in the LA that receive the conditioned stimuli (CS, audible sound) also receive inputs from the somatosensory cortex and thalamus delivering information about the aversive unconditioned stimulus (US). According to a currently held view, synaptic enhancements in the CS pathways, implicating the mechanisms of long-term potentiation (LTP), contribute to the encoding of the memory of the CS-US association (Maren and Quirk, 2004). Both fear conditioning and the ability of glutamatergic synapses in the CS pathways to undergo LTP are controlled by the strength of GABA-mediated inhibition in the LA (Fanselow and LeDoux, 1999; Shaban et al., 2006; Shin et al., 2006), thus demonstrating an essential role for GABAergic neurotransmission in plastic changes implicated in the acquisition of fear memory. In the present study, a particular form of NMDA receptor-dependent LTP, induced by theta burst stimulation, was selectively suppressed in cortical inputs to principal neurons in the LA, while significant LTP could be observed in inputs to interneurons. The authors provided evidence that the suppression of theta-stimulation-induced LTP in inputs to neurons was mediated by activation of GABAb receptors on glutamatergic terminals in the course of LTP-inducing stimulation. Therefore, the target-specific suppression of synaptic transmission in the LA, preventing the induction of LTP in the CS pathway (cortical input to principal neurons), could contribute to the maintaining of the inhibitory prevalence in the LA. At the behavioral level, this could help to avoid generalized fear responses to the nonharmful stimuli. Although the reported findings are clearly of significant importance, it would be necessary to demonstrate in future studies that such mechanisms are, in fact, recruited behaviorally during the acquisition of fear memory to auditory stimulation.

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