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Short-Term Depression at Thalamocortical Synapses Contributes to Rapid Adaptation of Cortical Sensory Responses In Vivo

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Summary

In vivo whole-cell recordings revealed that during repeated stimulation, synaptic responses to deflection of facial whiskers rapidly adapt. Extracellular recordings in the somatosensory thalamus revealed that part of the adaptation occurs subcortically, but because cortical adaptation is stronger and recovers more slowly, cortical mechanisms must also contribute. Trains of sensory stimuli that produce profound sensory adaptation did not alter intrinsic membrane properties, including resting membrane potential, input resistance, and current-evoked firing. Synaptic input evoked via intracortical stimulation was also unchanged; however, synaptic input from the somatosensory thalamus was depressed by sensory stimulation, and this depression recovered with a time course matching that of the recovery of sensory responsiveness. These data strongly suggest that synaptic depression of thalamic input to the cortex contributes to the dynamic regulation of neuronal sensitivity during rapid changes in sensory input.

Introduction

Physiological studies reveal that adaptation is a common feature of cortical responses to visual (Ohzawa et al., 1982), auditory (Shu et al., 1993), olfactory (Wilson, 1998), and somatosensory stimuli (Hellweg et al., 1977; Ahissar et al., 2000, 2001). Functionally, adaptation may help allow the limited response range of neurons (0 to ~100 Hz) to encode sensory signals with much larger dynamic ranges by shifting the range of stimulus amplitudes over which neurons respond to match the prevailing stimulus conditions (Barlow and Földiák, 1989; Adorján et al., 1999; Müller et al., 1999; Fairhall et al., 2001). Stimuli that produce adaptation of neuronal responses can also have profound perceptual consequences on the appearance of subsequent stimuli (Blakemore and Campbell, 1969). Although adaptation occurs at multiple stages of each sensory pathway, it is often stronger and more stimulus specific at cortical rather than subcortical stages. The time scale over which adaptation builds up and recovers depends on the time course of stimulation. Brief stimulation produces adaptation which occurs and recovers rapidly (Nelson, 1991a; Bonds, 1991; Müller et al., 1999), while more prolonged stimulation can produce slower and more lasting forms of adaptation (Greenlee et al., 1991).

Despite their perceptual importance, the cellular and synaptic mechanisms contributing to sensory adaptation in the cortex are only partially understood. In cat primary visual cortex, prolonged (30 s to several minutes) exposure to high contrast stimuli produces a membrane hyperpolarization (Carandini and Ferster, 1997), which may reflect activation of a sodium-dependent potassium current (Sanchez-Vives et al., 2000a, 2000b).

Synaptic mechanisms, such as enhancement of inhibition (Dealy and Tolhurst, 1974) or depression of excitatory synapses (Finlayson and Cynader, 1995; Todorov et al., 1997; Chance et al., 1998; Adorján et al., 1999), have also been proposed as mechanisms for adaptation. Primarily, however, these hypotheses have been based upon in vitro slice studies and/or neural simulations. In vivo experiments have ruled out enhanced inhibition, since iontophoretic application of $GABA_A$ antagonists did not block rapid (Nelson, 1991b) or slower forms of adaptation in visual cortex (DeBruyn and Bonds, 1986). However, the hypothesis that synaptic depression contributes to adaptation has not been adequately tested.

Simulations based on in vitro measurements suggest that short-term depression could lead to adaptation of cortical sensory responses either by reducing thalamocortical input to the cortex or by reducing the degree of amplification of that input by diminishing recurrent excitation among cortical neurons (Todorov et al., 1997; Chance et al., 1998).

Here, we investigate the relationship between synaptic and sensory dynamics in the rat whisker barrel cortex (also known as the posteromedial barrel subfield). Firing of neurons in rat primary somatosensory cortex, like that of cortical neurons in other mammalian primary sensory areas, adapts strongly during repeated stimulation (Armstrong-James et al., 1993; Ahissar, et al., 2000, 2001). In order to investigate the mechanisms underlying this adaptation, we performed in vivo whole-cell recordings from individual neurons in the barrel cortex and measured synaptic responses to whisker deflection and to electrical stimulation of the thalamus.

Results

Rapid Adaptation of Responses to Whisker Deflection

Simultaneous extracellular recordings were obtained from neurons in the ventroposteromedial nucleus (VPM) of the thalamus and the barrel cortex that responded optimally to stimulation of the same principal whisker (Figure 1A). During 5 s long trains of 4 Hz deflection, VPM neurons exhibited modest adaptation (34% ± 14%, n = 10), while cortical neurons adapted more strongly (80% ± 2%, n = 6) (Figure 1E). The same trend was observed in a few single units large enough to be well isolated from multiunit firing activity. At 4 Hz, the firing rate of VPM single units adapted by 33% ± 2% (n = 7),

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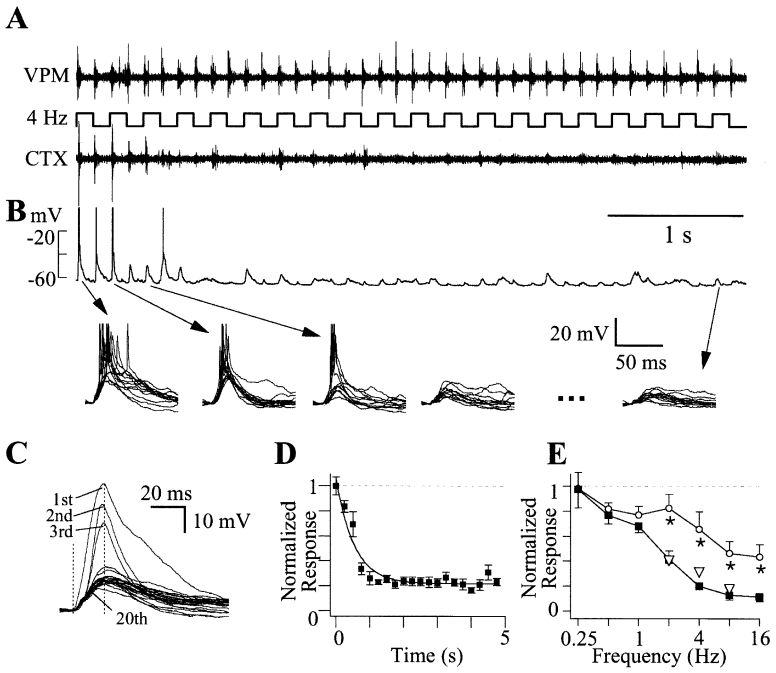

Figure 1. Rapid Adaptation of Whisker Responses in Thalamus and Cortex

(A) Simultaneous extracellular multiunit recordings from barrel cortex (CTX) and thalamus (VPM) during 4 Hz stimulation of the primary whisker (B1). The depth of the cortical recording was 390 μm.

(B) Intracellular responses of a cortical neuron in the C1 barrel to a 4 Hz stimulation of the primary whisker. The depth of recording was 470 μm. Upper trace is a single trial. Multiple repetitions (n = 12) of the first four and the last onset responses in the train are shown below at expanded time scale.

(C) Average of responses shown in (B) after median filtering to remove spikes. The sensory latency was 7 ms. Response amplitude was measured as the difference between the two dotted lines.

(D) Onset response amplitudes normalized to the first response. Bar indicates ± SEM. Fit is a single exponential (τ = 0.54 s, steady state = 21%).

(E) Frequency dependence of rapid adaptation in barrel cortex and thalamus. Adaptation was significantly stronger in cortical firing (■; n = 6) than thalamic firing (○; n = 10) at stimulating frequencies equal to or higher than 2 Hz (one tailed t test, $p < 0.005$, indicated by asterisks). Adaptation of cortical intracellular responses (▽; n = 9, 61, and 48 for 2, 4, and 8 Hz) was comparable to that of cortical firing. The SEM of some data points is too small to be seen.

and cortical single units adapted by 87% ± 2% (n = 6) (data not shown). The adaptation occurred rapidly, so that after the first few deflections, many cortical neurons ceased firing completely. We refer to this form of adaptation as "rapid adaptation" to distinguish it from slower forms of adaptation studied in other cortical regions (Ohzawa et al., 1982; Carandini and Ferster, 1997). Here we use rapid adaptation to refer specifically to responses to repetitive whisker deflection and not to the "rapidly adapting" or "phasic" response to a single deflection (Waite, 1973; Shipley, 1974).

Rapid adaptation of firing rate was frequency-dependent, with higher stimulating frequencies yielding more pronounced adaptation (Ahissar et al., 2001). Figure 1E shows normalized steady-state adaptation as a function of stimulating frequency. Although both exhibited frequency-dependent adaptation, VPM neurons adapted strongly only at higher stimulating frequencies (Figure 1E , open circles). At all frequencies tested above 1 Hz, cortical responses (Figure 1E , closed squares) adapted significantly more strongly than thalamic responses (one tailed t test, $p < 0.005$; Figure 1E, asterisks). This suggests that, as in visual cortex (Ohzawa et al., 1982; Nelson, 1991a, 1991b), additional cortical mechanisms contribute to adaptation. In order to investigate these mechanisms further, we made whole-cell current-clamp recordings from individual neurons in barrel cortex. This permitted measurement, not only of the output of the cell, but also of changes in its synaptic input and its intrinsic membrane properties during and after rapid adaptation.

We obtained in vivo whole-cell recordings from a total of 114 barrel-cortex neurons. Recordings from 61 of these neurons were held long enough to permit adaptation of responses to be studied in detail. Most (53/61) were recorded at depths of 260–800 μm, corresponding to layers 2/3 and 4. The remaining eight neurons were recorded at depths of 800–1000 μm, presumably corresponding to upper layer 5. A subset of our sample (42/61) were classified on the basis of their firing in response to injected current (Moore and Nelson, 1998; Zhu and Connors, 1999). The majority of these cells were regular spiking (RS, n = 32), with a small number of cells exhibiting intrinsic bursting (IB, n = 7) or fast spiking (FS, n = 3) firing patterns. The remaining cells showed behavior that was intermediate between IB and RS firing, or they were not tested with injected current. No consistent differences were noted in sensory responses as a function of firing type, although our ability to detect differences may have been limited by the small sample of IB and FS cells. Roughly 80% of the neurons tested (48/61) fired action potentials in response to whisker deflection, and this fraction did not vary significantly with recording depth or response latency. Responses remained subthreshold in the remaining 13/61 neurons. Including these cells, the average firing was 1.23 ± 0.24 impulses/stimulus for the initial onset response.

Intracellular correlates of rapid adaptation are illustrated in Figures 1B–1D. The principal whisker was deflected at 4 Hz for 5 s. The latency of the sensory-evoked synaptic response was 7 ms, suggesting monosynaptic input from the thalamus (see Figure 3). Rapid adaptation of whisker-evoked synaptic potentials observed in individual traces (Figure 1B) was measured quantitatively from responses averaged across 12 repetitions of the entire stimulus train. To facilitate measurement of under-

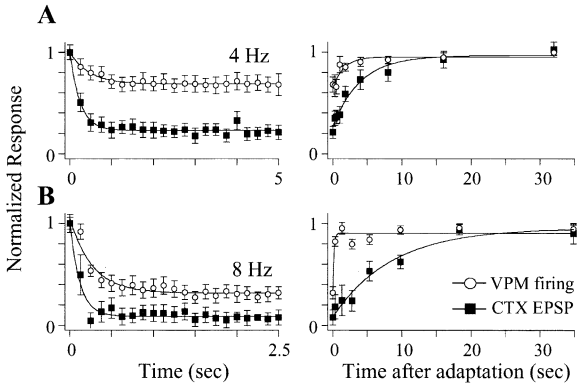

Figure 2. Kinetics of Adaptation and Recovery in Thalamus and Cortex

(A) Averaged adaptation (left) and recovery (right) of cortical intracellular responses (■; n = 11) and thalamic extracellular responses (○; n = 13) to a 4 Hz, 5 s train of whisker deflections and to individual test deflections delivered at various times after the train. Curves are single exponential fits to data points. Cortical responses adapt more rapidly and more completely than thalamic firing. Cortical intracellular responses also recover more slowly than thalamic firing.

(B) Averaged adaptation (left) and recovery (right) to an 8 Hz, 2.5 s stimulation (n = 9). Although cortical and VPM recordings were obtained simultaneously, a stronger stimulus was used for 8 Hz than for 4 Hz.

lying synaptic potentials, action potentials were removed with a median filter (see Experimental Procedures). Sensory responses dramatically decreased in size for the first three to four stimuli and then reached a steady state (Figures 1C and 1D). Steady-state responses adapted to 21% of original with a rate constant of 0.54 s or 2.2 stimuli. Adaptation was associated with a reduction of the earliest portion of the response (Figures 1B and 1C). The early response was reduced in slope, but did not change in latency (Figure 1C). Rapid adaptation of whisker-evoked synaptic responses was observed in all cells tested, although the magnitude varied across cells (see Figure 3B). The frequency dependence of this adaptation was comparable to that measured extracellularly (open triangles in Figure 1E).

Kinetics of Adaptation and Recovery

The kinetics of the onset of rapid adaptation at 4 and 8 Hz and subsequent recovery of responsiveness were studied in cortical intracellular and thalamic extracellular recordings (Figure 2). At 4 Hz, steady-state thalamic responses (n = 13) adapted by 31% ± 9% with a time constant of 0.47 s, while cortical synaptic responses (n = 11) adapted more strongly (79% ± 6%) and more rapidly (τ = 0.25 s) (Figure 2A). The time course of recovery from adaptation was tested by presenting single test stimuli at delays of 0.25 to 32 s after the offset of the adapting train. At 4 Hz, the recovery was well fit by a single exponential with a time constant of 1.58 s for thalamic firing and 3.97 s for cortical intracellular responses. At 8 Hz, as at 4 Hz, adaptation was stronger (93% ± 5% versus 70% ± 6%) and more rapid (0.12 versus 0.27 s), and recovery was much slower (8.52 versus 0.15 s) for cortical intracellular responses than for thalamic firing (n = 9). Thus, cortical intracellular responses adapt more quickly and recover more slowly than thalamic firing. These data, together with the greater magnitude of adaptation in cortex, suggest that adaptation is not solely due to subcortical mechanisms, but also depends upon additional cortical mechanisms.

Adaptation in Cells Receiving Direct Thalamic Input

Cortical circuits are highly recurrent, and therefore, response properties such as adaptation may arise from the interplay of multiple classes of synaptic inputs. Nevertheless, much has been learned both in the visual system (e.g., Ferster et al., 1996) and somatosensory system (Simons and Carvell, 1989) about thalamocortical response transformations by studying cortical neurons that receive direct thalamic input. In the rat barrel cortex, extracellular studies have identified thalamorecipient neurons on the basis of their laminar position (layers 4 and 5b) and by the brief and relatively constant latency of their sensory responses. To better understand the relationship between thalamic and cortical adaptation properties, we separated cortical neurons into neurons that presumably receive direct VPM input and neurons that presumably do not receive such input on the basis of response latency and compared adaptation in the two groups.

Cells were classified as neurons with presumptive monosynaptic input from the VPM if the latency of the synaptic response to deflection of the primary whisker was ≤8.5 ms (n = 38/109). In a subset of cells (n = 65), we also obtained the latency of the synaptic response to electrical stimulation of the VPM. Neurons were classified as receiving direct monosynaptic input from the VPM if they responded with a brief (≤2.5 ms) and constant latency (<1 ms jitter) to electrical stimulation. Example EPSPs evoked electrically and with sensory stimulation are shown in Figures 3C–3F for a neuron meeting these criteria and for another neuron that did not. The electrical latency of all but one of the neurons with early sensory responses was ≤2.5 ms (n = 20/21; below horizontal line in Figure 3A), suggesting that these do indeed correspond to neurons receiving direct thalamic input. In general, the sensory latency and latency to electrical stimulation were well correlated (slope = 0.97, r = 0.68; Figure 3A).

Figure 3B shows the distribution of steady-state adaptation as a function of the sensory latency for the same 61 cells in which rapid adaptation was measured from their intracellular responses. The observed negative relationship (slope = −0.046, r = −0.58) suggests that neurons that receive monosynaptic input from the VPM exhibit less adaptation than neurons that do not. This was equally true for the subsets of cells classified as IB (n = 7; Figure 3B, closed triangles) and RS (n = 32; Figure 3B, closed circles). The relationship could not be adequately assessed for FS cells (Figure 3B, closed squares) since all three recorded had short sensory latency.

Rapid Adaptation Does Not Alter Intrinsic Membrane Properties

Recent studies of contrast adaptation in the visual cortex have revealed that prolonged visual stimulation causes membrane hyperpolarization (Carandini and Ferster, 1997; Sanchez-Vives et al., 2000a). This hyper-

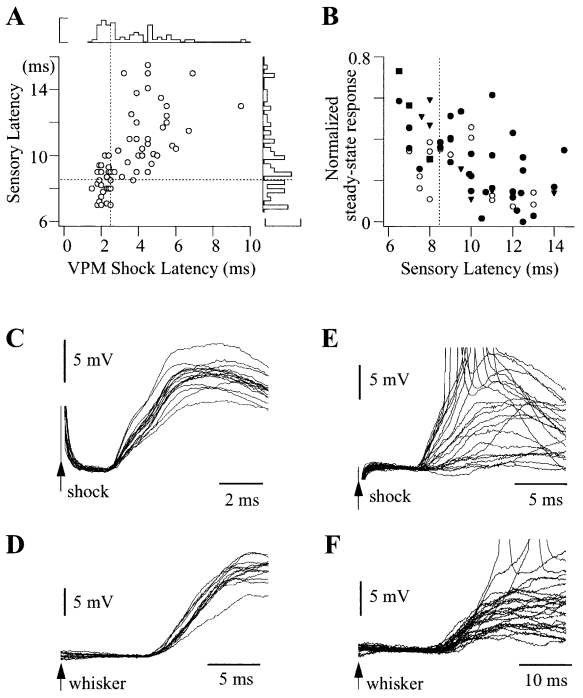

Figure 3. Electrical and Sensory Latencies of the Neurons with and without Direct Thalamic Input

(A) Scatter plot of sensory latency as a function of electrical latency. Latency measured from the whisker deflection in 65 neurons showed a direct relationship with latency measured from the electrical shock applied in the VPM. The sensory latency histogram is shown on the right and the electrical latency histogram above (bin size = 0.25 s). Scale bar for both histogram indicates 10 spikes. Twenty-one neurons had sensory latencies less than 8.5 ms (below horizontal line), twenty of which had electrical latencies ≤ 2.5 ms (left to vertical line). These neurons were classified as receiving direct VPM input.

(B) Dependence of steady-state adaptation on sensory latency. A negative relationship was observed between the level of steady-state adaptation and sensory latency (slope = −0.046, r = 0.58) in the same 61 neurons as in Figure 1E. The firing pattern was classified as regular spiking (●; n = 32), intrinsic bursting (▼; n = 7), fast spiking (■; n = 3), or was unclassified (○; n = 19).

(C and D) Electrical and sensory responses of a neuron with direct thalamic input. The latency was 2.2 ms and 8 ms for the electrical and whisker stimulation, respectively.

(E and F) Electrical and sensory responses of neurons that did not receive direct thalamic input. The electrical latency was 5.4 ms and the sensory latency was 14.3 ms.

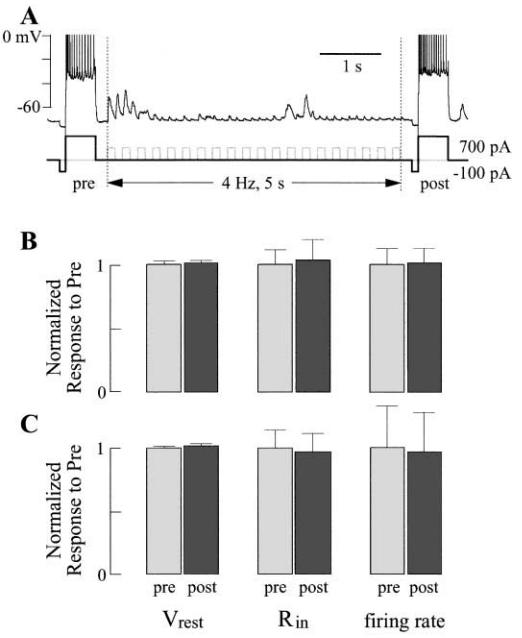

Figure 4. Rapid Adaptation Does Not Alter Intrinsic Properties of Cortical Neurons

Resting membrane potential (V_{rest}), input resistance (R_{in}) measured from the response to a brief hyperpolarizing current pulse (100 pA), and excitability measured from firing rate during a 500 ms long depolarization (500–1000 pA) was compared before and immediately after a 4 Hz, 5 s adapting stimulus.

(A) Example trace. Despite profound adaptation of EPSPs evoked by whisker deflection, response to current injection was unchanged (spikes truncated at 0 mV).

(B) Population results (n = 22). Normalized resting membrane potential, input resistance, and firing in response to current injection were not altered following rapid adaptation.

(C) Cortical neurons with direct VPM input (n = 8/22). Intrinsic properties also did not change significantly for these neurons.

polarization can be at least partially accounted for by a prolonged afterhyperpolarization (AHP) mediated by a sodium-dependent potassium current (Sanchez-Vives et al. 2000b). In order to determine whether or not a similar mechanism might contribute to rapid adaptation in somatosensory cortex, we measured the membrane potential before and immediately after induction of adaptation. As shown in Figure 4B, there was no difference in membrane potential (−61.7 ± 1.3 versus −62.1 ± 1.4 mV, n = 22). This was true both for sensory stimuli that, as in Figure 4A, produced only subthreshold responses (n = 8) and for sensory stimuli that produced suprathreshold responses (n = 14).

Activation of potassium currents in visual cortical neurons is associated with decreased input resistance near rest (Sanchez-Vives et al., 2000b). Decreased input resistance can also occur from a build up of GABAergic inhibition (Staley and Mody, 1992; Borg-Graham et al., 1998). In order to determine whether either of these mechanisms contributes to rapid adaptation, input resistance was measured before and after adapting stimuli. Because of the high series resistances sometimes associated with in vivo recording, we took care to correct for series resistance offline by fitting double exponentials to the responses to current steps (Borg-Graham et al., 1998; Hirsch et al., 1998; Anderson et al., 2000). Resting input resistance measured from the response to a brief 100 pA hyperpolarizing pulse was unchanged following adaptation (42.5 ± 4.8 versus 43.9 ± 6.7 MΩ, n = 22; Figure 4B). This argues strongly against a build up of GABAergic inhibition producing significant shunting; however, it does not entirely rule out a build up of potassium currents, since the hyperpolarizing current pulses used to measure input resistance themselves might decrease activation of these currents.

Further evidence against the involvement of postsynaptic potassium conductances was obtained from recordings (n = 8) in which the pipette solution contained cesium as the primary cation and the lidocaine derivative QX-314 to block spiking and $GABA_B$-mediated responses (Connors and Prince, 1982; Nathan et al., 1990).

Resting membrane potential depolarized to −36.5 ± 2.6 mV over the course of 10–20 min, and action potentials broadened, indicating significant reduction of potassium currents responsible for resting membrane potential and action potential repolarization. These neurons still exhibited robust adaptation with no evidence of hyperpolarization (steady state was 10.4% ± 3.4% of initial response at 4 Hz adaptation; data not shown).

In addition to measuring membrane potential and input resistance, we assessed membrane excitability by measuring the firing rate during a 0.5 s depolarizing pulse (500–1000 pA). Like the other cellular properties measured, excitability did not change (15.6 ± 1.8 versus 15.7 ± 1.8 spikes/s) following adaptation (Figure 4B; n = 22). There was also no effect of adaptation on the initial firing evoked during the first 50 ms of the depolarizing pulse (34.5 ± 3.7 and 37.4 ± 9.0 spikes/s). We could not rule out the possibility of very subtle changes in excitability, which might have been revealed with just suprathreshold current steps or with more complete characterization of the F-I curve, but such changes would be unlikely to account for the dramatic reduction in sensory responses observed. These results argue strongly that postsynaptic factors, including AHP currents or a build up of GABAergic inhibition, are unlikely to account for the dramatic reduction in sensory responses observed during rapid adaptation.

Neurons that do not receive direct thalamic input may inherit adaptation properties from those that do. Therefore, it is crucial to examine the mechanisms of adaptation in neurons receiving direct thalamic input. We looked for changes in intrinsic properties in a subset of cells in which the sensory latency was less than 8.5 ms (n = 6/22). As found for the entire population, there was no significant difference in membrane potential (−60.3 ± 0.7 versus −61.3 ± 1.0 mV), input resistance (42.3 ± 6.0 versus 41.0 ± 6.1 MΩ), or firing in response to current injection (12.5 ± 4.2 and 12.1 ± 3.9 spikes/s) measured before and after adaptation (Figure 4C). Therefore, it appears that in neurons receiving direct thalamic input, as well as in those without such input, rapid adaptation is due neither to intrinsic changes in membrane potential, nor to excitability, nor to build up of shunting inhibition.

Sensory Adaptation Is Not Consistently Accompanied by Depression of Intracortical Synapses

We and others hypothesized previously that adaptation may result in part from short-term depression at excitatory synapses (Finlayson and Cynader, 1995; Todorov et al., 1997; Chance et al., 1998; Galarreta and Hestrin, 1998). Cortical responses to sensory stimuli depend both on thalamocortical excitation and on recurrent excitation, which, even within layer 4, provides significant amplification (Douglas et al., 1995; Chung and Ferster, 1998). If our hypothesis is correct, sensory adaptation should produce depression of electrically evoked EPSPs. We tested this idea separately for excitatory inputs evoked intracortically and from the VPM. To test intracortical excitatory synapses, we stimulated layer 3 or 4 of the cortex near the recorded cell through a tungsten electrode. (We attempted to place the stimulating electrode within the same column, and lateral displacements were within 300–500 μm.) Stimulus strength was adjusted for each cell to produce a stable subthreshold response and then was not changed. After obtaining baseline responses to the electrical stimulus, the principal whisker was deflected at 4 Hz for 2.5 or 5 s. Individual electrical test stimuli were then given at various times beginning 0.25 s after adaptation.

Figure 5 shows an example experiment. Intracortical electrical stimulation evoked an averaged response of 11 mV (n = 14; Figure 5A). Rapid adaptation was induced by whisker stimulation at 4 Hz for 2.5 s (Figure 5B), which reduced sensory responses to 21% of the original (Figure 5C). Electrical stimuli were applied 0.25 and 2 s after the end of adapting train (Figure 5D). The initial, presumed monosynaptic component of the electrical response (difference between broken lines, n = 14 repetitions) was nearly identical before and after adaptation (open triangles in Figure 5E). Later, presumably polysynaptic components were, however, reduced. A reduction in spontaneous subthreshold synaptic input was often observed following sensory adaptation (data not shown). The loss of this input may have brought EPSPs evoked by the electrical stimulus below threshold in some neurons that provided polysynaptic input to the recorded neuron prior to adaptation.

No consistent change in the early response to cortical stimulation was observed across the 17 cortical neurons tested. The summary is shown in Figure 5E (closed squares). Rapid adaptation that reduced sensory responses by 74% ± 5% (data not shown) did not significantly reduce the size of the early slope of the EPSP evoked by cortical electrical stimulation. This suggests that rapid adaptation cannot be accounted for by a change in the efficacy of excitatory synapses formed between cortical neurons.

Sensory Adaptation Depresses Thalamocortical Synapses

In vitro, thalamocortical synapses have high probabilities of release and are strongly depressing (Gil et al., 1997, 1999; Stratford et al., 1996). In order to determine whether or not depression of thalamocortical synapses might contribute to rapid adaptation of sensory responses in vivo, we recorded thalamocortical EPSPs in barrel-cortex neurons evoked by stimulating locally within the corresponding barreloid of the VPM.

An example experiment is shown in Figure 6. Electrical stimulation of the VPM evoked a 4 mV monosynaptic EPSP with a latency of 1.8 ms (n = 30; Figure 6A). Adaptation at 4 Hz for 2.5 s reduced the sensory response by 54% (Figures 6B and 6C). Electrical stimuli delivered to VPM at various times following the train of sensory stimuli evoked smaller responses. The initial monosynaptic thalamocortical EPSP was reduced by 40% 0.25 s after adaptation. An exponential fit to all responses evoked after the train of sensory stimuli revealed a recovery time constant of 1.85 s (open triangles in Figure 6E). Unlike the responses to cortical stimulation, reduction in the earliest portion of the response was evident, and the slope of the rising phase was decreased (Figure 6D).

We performed a similar experiment on ten barrel-cor-

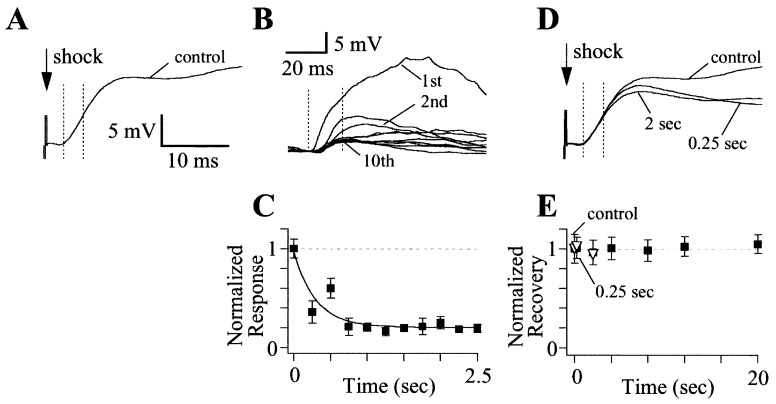

Figure 5. Rapid Adaptation Does Not Alter Electrically Evoked Intracortical EPSPs

(A) Average EPSP (n = 14) evoked in a cortical neuron by intracortical stimulation before adaptation. Latency was 2.5 ms. The amplitude of the presumed monosynaptic component measured during initial rising phase (difference between dotted lines) was 4 mV.

(B and C) Rapid adaptation of responses to 4 Hz, 2.5 s whisker deflection. Steady-state sensory responses were reduced by 80% (τ = 0.30 s).

(D) Average EPSP evoked in a cortical neuron by intracortical stimulation after adaptation. Amplitudes of early components of EPSPs electrically evoked 0.25 and 2 s after adaptation were nearly unchanged (102% and 96% of control, open triangles in [E]). The scale is the same as in (A).

(E) Average results obtained from 17 neurons (■) and the cell shown in (A)–(D) (▽). Adaptation reduced sensory responses by 74% ± 5%, but did not change the amplitude of the early component of the intracortical EPSP evoked electrically at all the time points measured later.

tex neurons that received monosynaptic input from VPM. Rapid adaptation at 4 Hz for 2.5 s reduced the sensory response by 64% ± 4% (data not shown). In these same cells, responses to electrical stimulation of VPM were reduced by 27% ± 5% at 0.25 s after adaptation and recovered with a time constant of 4.98 s (single exponential fit; closed squares and solid line in Figure 6E). This rate of recovery is similar to that observed for cortical intracellular responses to single whisker deflections (3.97 s; right panel in Figure 2A). This demonstrates that, during rapid adaptation, thalamocortical synapses undergo short-term depression, which recovers with a rate similar to that of sensory responses. Taken together, our results strongly suggest that depression at thalamocortical synapses is an important component of the biophysical mechanism of rapid adaptation.

Discussion

The experiments described here strongly suggest that short-term synaptic depression, a feature of cortical synapses widely studied in vitro, contributes to rapid adaptation of sensory responses in vivo. Surprisingly, cortical stimulation did not reveal a contribution of depression at recurrent excitatory synapses to rapid adaptation. Instead, repeated sensory stimulation appears to temporarily decrease the gain of thalamocortical synaptic transmission. These findings, together with our measurements of intrinsic properties of cortical neurons before and after adaptation, indicate that rapid adaptation in somatosensory cortex occurs by a different mechanism than that previously identified for slower forms of adaptation in cat and ferret visual cortex.

Extracellular recordings in VPM conducted in this study and in prior studies (Diamond et al., 1992; Sosnik et al., 2001) suggest that a portion of cortical adaptation can be accounted for by a mechanism already operating at the level of the thalamus. Recordings made at earlier stations of the trigeminal system (Shipley, 1974; Sosnik et al., 2001) suggest that this adaptation is not inherited from the trigeminal input, but is generated intrathalamically (although the presence of thalamic adaptation over this frequency range may depend on stimulus duration, anesthesia, and perhaps other factors; see Diamond et al., 1992; Hartings and Simons, 1998; Ahissar et al., 2001). This thalamic form of adaptation could reflect

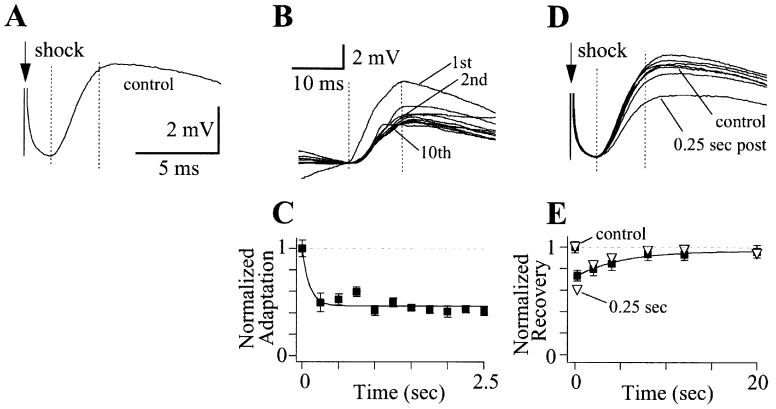

Figure 6. Rapid Adaptation Depresses Thalamocortical Synapses

(A) Average EPSP (n = 30) evoked in a barrel cortical neuron by electrical stimulation of the corresponding barreloid in VPM before adaptation. Electrical stimulation in layer 3 or 4 of nearby cortex evoked an EPSP sized 4 mV with a latency of 1.8 ms, consistent with monosynaptic input from VPM.

(B and C) Rapid adaptation to 4 Hz, 2.5 s whisker deflection. Adaption reduced sensory responses by 54%.

(D) Average EPSPs evoked by electrical stimulation of the corresponding barreloid in VPM at 0.25, 2, 4, 8, 16, and 20 s after adaptation. The response to thalamic shock 0.25 s after offset of the adapting train was reduced by 40%. Additional trials, in which longer recovery periods were allowed, revealed a recovery time constant of 1.85 s (▽ in [E]). The scale is the same as in (A).

(E) Average results obtained from 10 neurons (■) and the cell shown in (A)–(D) (▽). Adaptation to a 4 Hz, 2.5 s whisker stimulation reduced responses by 64% ± 4% (data not shown). Reponses to VPM shock recovered with a time constant of 4.98 s (solid curve).

depression at afferent synapses, which, by analogy with retinogeniculate synapses, might be expected to have high probabilities of release (Chen and Regehr, 2000) and hence exhibit depression. Alternatively, the thalamic adaptation could reflect feedback inhibition from the reticular nucleus, intrinsic firing properties of thalamic neurons (McCormick and Feeser, 1990), or the withdrawal of excitatory cortical feedback.

Comparison of adaptation in cortical and thalamic neurons strongly suggests that an additional intracortical mechanism reduces the response to repetitive stimulation. Adaptation of cortical responses was stronger and recovered more slowly (Figure 2). Several points of evidence argue that this is not due to a build up of postsynaptic inhibition (Dealy and Tolhurst, 1974), nor to activation of a potassium current like that hypothesized to underlie contrast adaptation in cat and ferret visual cortex (Sanchez-Vives et al. 2000b). First, like cortical action potentials, cortical EPSPs evoked by whisker deflection adapted more completely and recovered more slowly than VPM firing. This was true for the earliest portions of the response, which occurred with a latency (e.g., 7–8 ms) too rapid to be consistent with polysynaptic activation relayed through other cortical neurons. Second, although our sample was limited, synaptic responses in fast-spiking neurons also adapted. This is consistent with the observation that thalamocortical synapses onto cortical interneurons, like those onto excitatory neurons, are strongly depressing (Gibson et al., 1999). Third, adaptation did not significantly hyperpolarize the resting membrane potential or reduce the input resistance. Fourth, adaptation did not alter the firing produced by current injection. Finally, partial blockade of cellular potassium currents with cesium did not reduce adaptation.

Cells receiving direct VPM input exhibited less adaptation (Figure 3B). Adaptation in these neurons may bring their sensory responses below threshold, thus dramatically reducing excitatory input to other cortical neurons. In keeping with this, synaptic input to neurons not receiving direct VPM input was often completely abolished during adaptation, while small, subthreshold inputs were more typically preserved in cortical neurons with direct VPM input.

Unlike lemniscal thalamocortical input from VPM, paralemniscal input from the posterior thalamic nucleus (PO) reaches cortex at longer and more variable latencies (Diamond et al., 1992), and the latency increases dramatically with repeated stimulation and with increased frequency (Ahissar et al., 2000; Sosnik et al., 2001). The adaptation we observed is unlikely to reflect selective loss of paralemniscal input from PO, since we observed changes in the amplitude of the synaptic response with little change in latency, and since the adaptation was present in the earliest response components. Similarly, reduced corticothalamic feedback cannot account for adaptation of the earliest portion of the response. Loss of PO inputs or corticothalamic feedback could have contributed to adaptation of later response components, but it is difficult to disentangle these effects from those caused by loss of polysynaptic inputs mediated intracortically.

What accounts for the lack of membrane hyperpolarization during rapid adaptation in rat barrel cortex? One possibility is that adaptation has different mechanisms in different mammalian species (rodent versus carnivore) or in different cortical regions (somatosensory versus visual). While we cannot rule out the possibility of a species difference, preliminary experiments in rat visual cortex have revealed that rapid adaptation in response to flickering stimuli is also not associated with hyperpolarization or a change in input resistance, suggesting that differences between cortical regions are unlikely to account for the apparent discrepancy (X. Li et al., 2000, Soc. Neurosci., abstract). A more likely explanation is that rapid adaptation and slower forms of adaptation occur by different mechanisms. The rapid adaptation measured here occurs within a fraction of a second and recovers over the course of one to a few seconds. Rapid adaptation in visual cortex can be robustly induced by a single briefly flashed stimulus (Nelson, 1991a, 1991b; Bonds, 1991; Müller et al., 1999). On the other hand, membrane hyperpolarization was induced by much longer adapting stimuli (Carandini and Ferster, 1997; Sanchez-Vives et al., 2000a, 2000b). Psychophysical studies have revealed that, depending on the duration and perhaps other properties of the adapting stimulus, the time course of recovery from adaptation can vary from seconds to tens or hundreds of seconds (Maddess et al., 1988; Greenlee et al., 1991), and in some cases, even longer lasting effects have been described (Humphrey et al., 1995; Greenlee et al., 1991). Rapid adaptation and slower forms of adaptation, such as that associated with membrane hyperpolarization, may therefore represent distinct cellular mechanisms operating at different time scales. Multiple timescales of adaptation may be required to optimally encode time-varying stimuli (Fairhall et al., 2001).

Studies in neocortical slices have revealed that synapses between excitatory neurons are typically depressing. This is true for vertical inputs to layer 2/3 pyramidal neurons (Varela et al., 1997), connections between layer 5 neurons (Thomson et al., 1993; Tsodyks and Markram, 1997), and connections between layer 4 neurons (Stratford et al., 1996). However, the degree to which these synapses depress in vivo is not entirely clear. In visual cortex, for example, electrically evoked synaptic depression in adult cat (Sanchez-Vives, 2000a) and 4- to 5-week-old rat (Y. Zhou and S.B.N., unpublished data) is modest compared to that observed in vitro. In barrel cortex, the present results indicate that sensory adaptation does not depress intracortical excitatory synapses. This could in part reflect the fact that cortical neurons cease firing during the adapting train, allowing time for recovery from synaptic depression. In addition, different classes of cortical synapses may be heterogeneous with respect to depression, and this may obscure the contribution of depressing synapses in the average dynamics of the electrically evoked population response. It remains most likely, however, that cortical synaptic depression is less prominent in vivo than suggested by prior in vitro studies. This may represent a developmental reduction in depression as synapses mature (Varela et al., 1997; Reyes and Sakmann, 1999; Angulo et al., 1999) or could reflect other factors, such as differences in ionic concentrations or neuromodulatory state.

Thalamocortical synapses are among the most

strongly depressing synapses studied in vitro (Gil et al., 1997). In vivo, they can be either depressing or facilitating, depending on the particular pathway studied (Castro-Alamancos and Connors, 1996a), the frequency of stimulation (Morin and Steriade, 1981; Ferster and Lindström, 1985), and the behavioral state (Castro-Alamancos and Connors, 1996b). Our results show that thalamocortical synapses made by VPM neurons can indeed be depressed by sensory input in vivo.

Rapid adaptation is significant over stimulation frequencies that are well within the normal physiological range of this sensory system. Rats typically whisk at 5–10 Hz during active exploration. We observed significant adaptation at frequencies above 2 Hz. Note that the low frequency at which adaptation occurs may correspond to significantly higher thalamic firing frequencies. VPM neurons typically fired two or more action potentials at stimulus onset and one or two action potentials at stimulus offset. Therefore, stimulation at 4–8 Hz can cause thalamic firing of 15–30 spikes/s. Prior studies of responses to repetitive whisker stimulation have often used brief deflections that evoke a single fused response rather than separate onset and offset responses. This may account for the more modest adaptation observed at frequencies below ~10 Hz in prior studies (Diamond et al., 1992; Hartings and Simons, 1998).

We and others have speculated that the unadapted state may reflect heightened sensitivity for detection of small, transient stimuli (Fanselow and Nicolelis, 1999; Moore et al., 1999). This would serve the useful function of alerting quiescent, sleeping, or inattentive animals to the presence of an object within reach of their whiskers. During active exploration, sensitivity of detection may be sacrificed to enhance discriminability of similar stimuli. In support of the idea of enhanced discriminability, optical imaging experiments reveal that stimulation at low frequencies (e.g., 1 Hz) produces a much greater tangential spread of cortical activity than higher frequency stimulation (e.g., 5 Hz) (Sheth et al., 1998). Hence, at low frequencies, the cortical representation of two nearby whiskers show a much greater degree of overlap, while at higher frequencies, the magnitude of the cortical response is diminished, but so is the degree of overlap.

Responses of cortical and thalamic neurons to repeated stimulation may be strongly modulated by behavioral state, and therefore, the strength of the adaptation observed in the present study could reflect the depth of the anesthesia employed (Castro-Alamancos and Connors, 1996a, 1996b; Fanselow and Nicolelis, 1999). However, Swadlow and Gusev (2001) have recently reported that, even in the awake state, the efficacy of thalamocortical transmission is proportional to the length of the preceding interspike interval. Pauses in thalamic firing of up to 800 ms nearly doubled the efficacy of thalamic spikes in causing cortical firing. This suggests that the degree of adaptation is likely to be strongly influenced by spontaneous firing rates of thalamic neurons. When these rates are low, for example during the hyperpolarization of thalamic neurons that can accompany anesthesia and states of low arousal, strong adaptation will be observed. On the other hand, when spontaneous firing is high, during aroused or more lightly anesthetized states, less adaptation is expected since thalamocortical synapses will be in an initially depressed state (Castro-Alamancos, 1997). Functionally, the impact of this will be to enhance the temporal fidelity of transmission during periods of high activity by allowing the system to provide similar ouputs to inputs spaced narrowly in time (Fanselow and Nicolelis, 1999).

Experimental Procedures

Animal Preparation

Fifty-four Long Evans rats age P25–P35 were used in the experiments. Animals were anesthetized by IP injection of urethane (1.5 g/kg, 20% in distilled water). Atropine (60 mg/kg IM) was given to reduce respiratory secretions. The anesthetic state was maintained at a level at which there was no motor or cardiovascular response to toe-pinch with additional doses of urethane when needed. Animals were placed in a stereotaxic frame, and temperature, respiratory rate, and heart rate were monitored. Body temperature was maintained at 37°C with a feedback-controlled heating blanket. Craniotomies were performed over the left barrel cortex (Horsely-Clark coordinates: lateral, 4–6 mm; AP, 2–4 mm) and VPM (lateral, 2–4 mm; AP, 3–5 mm). After removing the dura, the cortex was covered with warm agar (3% in saline) to prevent drying and to reduce vascular pulsation.

Physiological Recording

Current-clamp recordings (Axoclamp 2B, Axon Instruments, Union City, CA) were performed using previously described methods for "blind" in vivo whole-cell recording (Ferster and Jagadeesh, 1992; Nelson et al., 1994). Patch pipettes (resistance 4–7 MΩ) were pulled in two stages on a horizontal puller (Sutter Instruments, Novato, CA) from borosilicate glass (Warner Instruments, Hamden, CT) and were filled with internal solution containing 130 mM methyl K^+-sulfate, 10 mM KCl, 10 mM K^+-HEPES, 2 mM $MgSO_4$, 0.5 mM EGTA, and 3 mM K^+-ATP (buffered to pH 7.3 and adjusted to 280 mOsm). Resting potentials were -66 ± 0.5 mV, and input resistance obtained offline after correction of series resistance was 50.5 ± 2.5 MΩ ($n = 114$).

Electrical and Sensory Stimulation of the Thalamus

Multiunit extracellular recordings were obtained from clusters of thalamic neurons using single tungsten electrodes (impedance of 0.1–1 MΩ). VPM was easily identified by the presence of robust, short latency (<10 ms) responses to deflection of the primary whisker. Electrode positions were adjusted so that cortical and thalamic recording sites were from the corresponding barrel and barreloid. Constant current electrical stimuli (0.1–0.5 mA, electrode negative) were delivered through the same tungsten electrode.

The primary whisker was deflected using a piezoelectric bimorph wafer (Piezo Systems, Cambridge, MA) attached to a glass pipette (Simons, 1983). The square-wave voltage at 0.25–16 Hz applied to the wafer was low-pass filtered ($\tau = 5$ ms) to avoid ringing. For most experiments, the amplitude of the deflection was ~200 μm, applied 1 cm from the base of the whisker. For the 8 Hz recovery data shown in Figure 2B, the amplitude of the deflection was doubled. Thalamic and cortical responses were recorded simultaneously and so are directly comparable, but since stimuli differed, recovery rates at 4 and 8 Hz are not directly comparable. The direction of the deflection was adjusted to optimize the response for each cell. Only onset responses were analyzed.

Data Analysis

Intra- and extracellularly recorded signals were digitized at 10 kHz (National Instruments) using routines written in the IGOR programming environment (Wavemetrics, Lake Oswego, OR). Poststimulus time histograms (PSTHs; bin size 1 ms or less) were constructed from spikes occurring within 30 ms after whisker deflection. Under our recording conditions, spontaneous firing was low, and therefore, evoked responses were not corrected for the possible inclusion of spontaneous spikes. Adaptation was measured as the ratio of the average responses during the last three stimulus cycles to the re-

sponse during the first stimulus cycle. Latency was defined as the time at which the PSTH deviated from zero.

Action potentials were removed from intracellular traces by replacing each data point by the median value of a moving boxcar window (5 ms) over the entire trace (median filter). Response amplitudes were measured as the difference between two 1 ms windows occurring immediately prior to response onset and during the rising phase of the averaged response (dotted lines in Figures 1C, 5, and 6). Measurements of peak or average velocity during the rising phase, or integrated response areas produced similar estimates of adaptation amplitude and time course (not shown). Intracellular response latency was measured from the intersection of linear fits to the baseline preceding the response and the rising phase of EPSPs.

Reported response latencies within the VPM and barrel cortex differ widely as a function of stimulation and recording conditions. For example, in VPM, average values range from 6–7 ms (Armstrong-James and Callahan, 1991; Friedberg et al. 1999) to 10–11 ms (Hartings and Simons, 1998; Sosnik et al., 2001; Brumberg et al., 1999). Within a layer 4 barrel, reported latencies are typically 2–4 ms later, ranging from ~10 ms (Welker et al., 1993) to ~14 ms (Brumberg et al., 1999). Under our recording and stimulation conditions, the earliest suprathreshold responses observed in the cortex occurred at 7–8 ms. We reasoned, therefore, that synaptic responses occurring prior to 8.5 ms were likely to be dominated by, if not exclusively due to, thalamocortical input.

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