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Effects of thalamic high-frequency electrical stimulation on whisker-evoked cortical adaptation

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Abstract

Activity in thalamocortical circuits depends strongly on immediate past experience. When the successive activity is attenuated on short timescales, this phenomenon is known as adaptation. Adaptive processes may be effectively initiated by ongoing exposure to sensory stimuli and/or direct electrical stimulation of neural tissue. Ongoing high-frequency electrical stimulation is increasingly employed as a treatment for a variety of neurological disorders. Neural stimulation with similar parameters to therapeutic electrical stimulation may modulate the way in which cortical neurons respond and adapt to sensory stimuli. Here, we studied the effects of high-frequency stimulation of the somatosensory thalamus on the transmission of sensory signals in thalamocortical circuits. We examined how whisker-evoked sensory inputs in layer IV cortical barrels are affected by concurrent 100 Hz thalamic electrical stimulation and how the latter modulates sensory-evoked adaptation. Even in the presence of ongoing thalamic stimulation, sensory transmission in thalamocortical circuits is maintained. However, cortical responses to whisker deflections are reduced in an intensity-dependent fashion and can be nearly abolished with high intensity currents. The electrical stimulation-induced reduction in cortical responsiveness likely reflects engagement of circuit mechanisms that normally produce sensory adaptation.

Keywords

Electrical stimulation; Adaptation; Somatosensory; Thalamocortical; Barrels; Whisker

Introduction

Information processing in the brain is adaptive, permitting neural systems to adjust to continually changing environmental sensory conditions. Response properties of cortical neurons are modified based on recent sensory history (Felsen et al. 2002; Khatri et al. 2004; Kohn and Movshon 2004), and in some conditions, adaptive response properties have been

shown to increase information transmission in cortical neurons (Sharpee et al. 2006; Gutnisky and Dragoi 2008) and, relatedly, to affect perception (Levinson and Sekuler 1976; Yao and Dan 2001). Interventions that regulate adaptation in feedforward neural circuits may be useful for improving deficient sensorimotor performance related to abnormal neuronal firing.

The rodent whisker-to-barrel system is well suited for studying cortical circuitry and how adaptive processes affect thalamocortical and intracortical transformations of information. Thalamocortical synapses, although more efficacious than intracortical synapses, exhibit higher levels of short-term depression (Gil et al. 1997). Adaptation during periodic stimulation can affect the magnitude and timing of cortical responses (Castro-Alamancos and Oldford 2002; Khatri et al. 2004). Adaptation also modifies spatial aspects of cortical receptive fields, focusing sensitivity onto the principal whisker (PW), or receptive field center (Sheth et al. 1998; Castro-Alamancos 2002) and decreasing between-whisker suppression (Katz et al. 2006; Higley and Contreras 2007). The degree of response suppression from prior response history is dependent on the behavioral state of the animal (Fanselow and Nicolelis 1999; Castro-Alamancos 2004).

Repetitive stimuli in the form of intracranial electrical current pulses are used to treat a variety of disease-related syndromes including epilepsy, depression, Tourette's syndrome, and obsessive-compulsive disorder (Temel and Visser-Vandewalle 2004; Johansen-Berg et al. 2007; McCracken and Grace 2007; Halpern et al. 2008). The mechanisms by which such interventions, called deep brain stimulation (DBS), work remain unclear, though it is likely that effects are system dependent (Anderson et al. 2003; Kringelbach et al. 2007; McCracken and Grace 2007). Electrical stimulation in sensory pathways may potentially be useful in modulating abnormal network activity in circuits that have been damaged or developmentally compromised (e.g., Simons and Land 1987; Shoykhet et al. 2005). It is currently unknown, however, how electrical stimuli delivered concurrently with sensory input can affect sensory-evoked responses and signal transmission in afferent circuits having a strong feedforward architecture.

Here, we examined how high-frequency electrical stimulation in the somatosensory thalamus of the rat whisker-barrel system affects sensory transmission and adaptation in thalamocortical circuits. In primary somatosensory cortex of rodents, identifiable clusters of layer IV neurons, called "barrels," receive focused afferent inputs from topographically corresponding groups of thalamic neurons, called barreloids, in the ventral posterior medial (VPM) nucleus (Woolsey and Van der Loos 1970). Barreloid and barrel neurons are readily activated by deflections of topographically corresponding whiskers. The thalamocortical system is thus well suited for detailed investigations of local circuit function and the transmission and transformation of afferent information (White 1978; Simons and Carvell 1989; Agmon and Connors 1991). We applied electrical pulses of 100 Hz focally to VPM alone and while concurrently deflecting the stimulated barreloid's PW. We found that such ongoing VPM stimulation diminishes concurrent whisker-evoked responses in the corresponding cortical barrel. This decrease is intensity dependent, and, at sufficiently high current intensities, the sensory-evoked cortical response is nearly abolished. The magnitude of the thalamic stimulation effect depends also on the presence or absence of concurrent afferent activity evoked by whisker deflections themselves. Thalamic electrical stimulation appears to exert its effects in the cortex by engaging circuit mechanisms that normally produce sensory adaptation during repetitive whisker deflections.

Methods

Surgery

Data were obtained from nine Sprague-Dawley adult female rats. Surgical procedures and maintenance of rats during recording sessions, approved by the University of Pittsburgh IACUC, are similar to those previously described (Simons et al. 2007). In brief, rats were anesthetized with isoflurane, and a tracheal tube was inserted to maintain a clear air passage. Small diameter silastic tubing was inserted into the external jugular vein for drug delivery, and a small Teflon catheter was inserted into the right femoral artery for monitoring blood pressure. The skull was exposed, and small stainless steel screws were inserted into the bone, making contact with the cortical surface, over the contralateral occipital and frontal lobes for electrocorticogram (ECoG) monitoring; an additional screw was inserted into the bone over the ipsilateral frontal lobe to serve as a reference for cortical microelectrode recordings as well as a ground for thalamic electrical stimulation. A small area ($\sim 3 \times 3 \text{ mm}^2$) of bone and dura overlying the right Vpm nucleus was removed as well as a smaller area ($< 0.5 \times 0.5 \text{ mm}^2$) overlying the right barrel cortex. Saline was periodically applied to an acrylic dam constructed around the craniotomies.

During the recording session, isoflurane was discontinued, and the rat was maintained in a lightly sedated and narcotized state using fentanyl (Baxter Healthcare Corp., Deerfield, IL; $10 \mu\text{g kg}^{-1} \text{ h}^{-1}$). The rat was immobilized with pancuronium bromide (SICOR Pharmaceuticals Inc., Irvine, CA; $1.6 \text{ mg kg}^{-1} \text{ h}^{-1}$) to prevent spontaneous whisker movements that could otherwise interfere with use of our whisker stimulators (below). Body temperature was maintained at 37°C using a servo-controlled heating blanket (Harvard Apparatus, Hollister, MA). Blood pressure, heart rate, tracheal airway pressure, and ECoG were monitored throughout the recording session with a personal computer using custom written software. If any of these indicators could not be maintained within normal physiological ranges, the experiment was terminated.

At the termination of an experiment, the rat was deeply anesthetized with sodium pentobarbital (100 mg/kg , iv) and transcardially perfused (2% paraformaldehyde and 1.5% glutaraldehyde in 0.1 M phosphate buffer) for cytochrome oxidase (CO) histochemistry. The cortex was cut tangentially ($40 \mu\text{m}$ sections), and the thalamus was sectioned coronally ($80 \mu\text{m}$ sections). Tissue sections were reacted for CO (Land and Simons 1985) and were counterstained with thionine. Using microdrive readings, signs of tissue disruption, and electrolytic lesions made during the experiment, recording sites were localized with respect to individual barrels. Because of the complex geometry of thalamic barreloids, no attempt was made to identify thalamic recording sites with respect to individual barreloids; rather they were simply confirmed to be within VPM.

Electrophysiology

The ventral posterior medial was stimulated in a location that corresponded topographically to the layer IV recording electrode site. These sites were identified at the outset of the experiment by physiological mapping with low impedance microelectrodes ($< 1 \text{ M}\Omega$). The PW was determined first for the cortical craniotomy site by identifying the whisker that evoked the strongest multi-unit responses to manual whisker deflections, with little or no response to adjacent whiskers. The topographically aligned thalamic barreloid was then similarly identified using a second microdrive and microelectrode; the latter was used subsequently to apply trains of electrical pulses to VPM (see below). Layer IV cells were identified by microelectrode depth readings and physiological criteria (Simons 1978; Brumberg et al. 1999); depth estimates and recording sites relative to the barrel field were later confirmed during histological analysis.

For cortical recordings, single tungsten microelectrodes (1–5 M Ω impedance, FHC, Bowdoin, ME) were inserted into layer IV of the barrel cortex using a hydraulic microdrive equipped with a digital counter. For unit recordings, signals were bandpass filtered between 300 Hz and 10 kHz, while local field potentials (LFPs) were obtained with filter settings of 1 Hz and 10 kHz. Electrophysiological waveforms were digitized at 32 kHz with a National Instruments data acquisition system and custom software written in LabView. The computer was also used for simultaneous stimulus control (below). Spikes were detected online using an amplitude threshold, and waveforms were parsed from the continuous record and stored on disk for further analysis using custom spike-sorting software written in LabView. The software allows for visualization of selected unit waveforms during the sorting procedure. Single units were identified using analyses based on the first two principal components of the spike waveform and on inter-spike interval criterion (Lewicki 1998).

In one LFP recording session, non-NMDA receptors in layer IV were blocked by application of 2 μ l of 1 mM CNQX dissolved in 9% NaCl. CNQX was delivered using a 10 μ l syringe having a 30 ga. beveled needle. The tip was advanced so that the CNQX was injected at the depth of layer IV (~800 μ m). During this experiment, we first mapped the barrel field, as above, before placement of the syringe. The recording microelectrode was removed, the syringe needle was inserted at a nearby site and the recording microelectrode was re-inserted. LFPs were obtained after needle insertion but prior to CNQX injection. CNQX was injected slowly over the course of 10 min, and 5 min later, we again collected LFPs. No procedures were used to prevent leakage or diffusion of the CNQX from the needle tip.

Whisker deflection and thalamic stimulation

Whiskers were mechanically deflected using a piezoelectric stimulator (Simons 1983), attached ~10 mm from the base of the whisker. Stimulus waveforms, stored on disk, were output at 10 kHz via an eight-channel, fast digital-to-analog converter (National Instruments). For each cortical unit, angular tuning was quantified by deflecting whiskers with a ramp-and-hold stimulus delivered in eight primary directions: 0°, 45°, 90°, 135°, 180°, 315°, and 270°. The stimulus consisted of a 0.7-mm deflection of 200 ms duration with onset and offset velocities of ~125 mm/s (averaged from baseline to peak). A unit's preferred direction was taken as the deflection angle that evoked the largest number of spikes during the first 20 ms of the response to deflection onset. Periodic whisker deflections were then delivered in the unit's preferred direction. Periodic stimuli, similar to those used previously (Khatri et al. 2004), consisted of brief deflections (duration of 10 ms, onset and offset velocities of ~140 mm/s with an amplitude of 0.7 mm) at repetition frequencies of either 10 or 20 Hz (Fig. 1a, top). Each stimulus trial lasted 3 s, with the periodic deflections, delivered for 2 s beginning 500 ms after trial onset.

Periodic whisker deflections were delivered alone or they were paired with electrical stimulation in VPM. For the latter, low impedance (0.5–1.5 M Ω) tungsten microelectrodes were used to deliver trains of biphasic pulses (each phase = 0.04 ms) at a frequency of 100 Hz (Fig. 1a, bottom). Pulses, generated in constant current mode by an isolated pulse stimulator (Model 2100, A-M Systems, Inc., Sequim, WA), were triggered by the same D/A board used also to output whisker deflection waveforms. Electrical pulses were delivered throughout the 3-s trial. Beginning 0.5 s after trial onset, a 2-s train of whisker deflections was delivered at 10 or 20 Hz. Every 10th (10 Hz deflections) or 5th (20 Hz deflections) electrical pulse occurred at the time of a whisker deflection onset (Fig. 1a). Because whisker-evoked thalamic responses have latencies of ~5 ms, the electrical pulses occurred just prior to the arrival in VPM of the sensory-evoked signal.

Electrical stimulation intensities ranged from 80 to 400 μ A; the maximum intensity of 400 μ A was based on preliminary experiments in which we identified the lowest current range

that nearly or entirely eliminated cortical responses to concurrent whisker deflections. For each single unit or LFP, data were collected for 15 trials of the aforementioned 3-s stimulus protocol; current intensity was held constant during each 15-block trial. Stimulus blocks in which current was delivered were interspersed with blocks in which no current was delivered; different current intensities were delivered in increasing or decreasing order.

Data analysis

Initial treatment of data consisted of removing electrical stimulus artifacts from the electrophysiological records. For unit recordings, any events that occurred 1 ms preceding and 1 ms following current impulse times were removed from the spike-time record. A consequence of this procedure is that any very short latency spikes evoked by the electrical stimulus itself were excluded from the analyses. Subsequent spike sorting eliminated any residual artifacts; these were relatively rare and occurred primarily with the higher current intensities. Identical procedures were used for unit records obtained during control trials in which currents of 0 μ A were used. This assured that spikes were analyzed during identical time epochs under all conditions. For LFP recordings, the electrical stimulation artifact was removed by subtracting, from trial-averaged waveforms, a template constructed by averaging electrical stimulation signals that were recorded at either the beginning and/or end of the experiment in the saline well, immediately outside the surface of the brain. When LFP recordings were used for measuring whisker-evoked responses, the template-subtracted waveform was low-pass filtered at 100 Hz followed by use of a bandstop filter between 90 and 110 Hz.

Artifact-purged spike time records were accumulated into peristimulus time histograms (PSTHs) having 2 ms bins. PSTHs were used to calculate the average number of spike counts per cycle of periodic whisker deflection; calculations were performed on a cycle-by-cycle basis. Stimulus-evoked average LFP amplitudes were quantified as peak-to-peak voltage (i.e., the difference between the highest and lowest voltage following a whisker deflection). Using a relative amplitude measurement, rather than absolute peak values, renders estimates of LFP magnitude more robust in the presence of low-frequency background noise (Colonnese et al. 2008). Tests of significance were accomplished using one-way ANOVA tests followed by Tukey's test for independent comparisons.

Quantitative measures of neural responses were examined to determine how thalamic electrical stimulation affected cortical responses to concurrent whisker deflections. For a given deflection velocity, held constant in the present experiments, periodic whisker stimuli are associated with progressively smaller evoked responses depending on the frequency of the deflections (Khatri et al. 2004). In order to quantify adaptation in cortical units, we calculated an adaptation index (AI) in which the spike count evoked by a given deflection cycle is divided by the spike count evoked by the first deflection in the train; a value <1.0 indicates response adaptation. The same procedure was applied to the cycle-by-cycle LFP magnitudes using peak-to-peak amplitudes. All analyses were performed using custom software in the LabView (National Instruments, Austin, TX) and Matlab (Mathworks, Natick, MA) environments.

Results

Thalamic electrical stimulation diminishes cortical response magnitude and adaptation

High-frequency electrical stimulation in VPM reduced the magnitude of whisker-evoked responses in the topographically aligned cortical barrel. Figure 1b shows raster plots, for example, cortical unit in response to 15 presentations of the 10 Hz periodic whisker stimulus. Without electrical stimulation (0 μ A), the unit showed low spontaneous firing and

highly phasic, time-locked responses to most, though not all, of the individual whisker deflections. When whisker deflections were accompanied by 320 μA pulses, the unit fired only sparsely. Early in the trial electrical stimulation, evoked spikes are evident. Such firing likely reflects multi-spike responses (bursts), because we eliminated the shortest-latency spikes from the analyses (see “Methods” section). Later in the stimulus train, fewer electrically evoked spikes occur. In some units, this elevated burst firing persisted into the 2 s of whisker deflection; this is evident in the bottom two raster lines in Fig. 1b, which correspond to the first two trials in the protocol. We eliminated potential confounds of such non-stationary effects by omitting the first five trials from the analysis of trial averaged data.

Similar reductions in whisker-evoked firing are evident in accumulated cycle-by-cycle responses. The PSTH of an example unit (Fig. 2a) exhibits reliable phasic responses to 10 Hz deflections in the control condition (0 μA). Firing was substantially diminished during concurrent 320 μA stimulation, resulting in some cases in a complete absence of spiking during some cycles (Fig. 2a, bottom). Whisker-evoked spikes, when they occurred, remained highly time-locked to the onset of each whisker deflection. In order to examine the effect of thalamic stimulation on the time course of whisker-evoked responses, we compared the PSTH associated with the first cycle of a 10 Hz whisker-deflection train to the PSTH averaged over later cycles. Figure 2b shows the initial-cycle PSTH and the late-cycle PSTH (averaged over cycles 11–20) for 0 μA current (top panel). Periodic 10 Hz whisker deflections by themselves produce modest sensory adaptation, observed here as a slower response onset and an overall reduction in total response magnitude of ~20%. When a 160 μA current is applied, both the initial and late cycle PSTHs are reduced in magnitude and become more similar in time course. The ratio of late-cycle to first-cycle firing is greater during response onset (first 5 ms) for 160 versus 0 μA currents (Fig. 2b, bottom); in other words, whisker-evoked adaptation is less pronounced, because the preceding electrical pulses have already placed the circuit in an adapted state.

We also examined LFPs under the assumption that they widely reflect neural activity in layer IV neurons near the recording electrode (Mitzdorf 1985). Figure 2c shows traces of whisker-evoked LFP responses to the first cycle of whisker deflection during concurrent electrical trains at different current intensities. Similar to PSTHs measured from single unit activity, e.g., Fig. 2b, the (peak-to-peak) amplitude of the LFPs evoked by the first whisker deflection decreases with increased current intensity. Data for three LFP recordings (different animals) and 22 single unit recordings are quantified in Fig. 2d. LFP data are plotted as peak-to-peak amplitude averaged over all whisker deflection cycles, and single unit data are plotted as the average spike count per cycle. For the largest thalamic stimulus current (320 μA) tested for this recording, the whisker evoked-LFP is reduced ~fourfold and the spike response is reduced ~2.5-fold. There were significant reductions in observed spike counts for all currents ≥ 240 μA ($P < 0.05$; one-way ANOVA with Tukey’s test). In the case of LFPs, response amplitudes were reduced for currents ≥ 160 μA ($P < 0.05$; one-way ANOVA with Tukey’s test). It is important to emphasize that these data quantify whisker-evoked responses, not electrical stimulus-evoked responses. There are, in fact, electrical stimulus-evoked field potential responses (as shown in the following sections), but for the present analyses such responses (and/or stimulus artifacts) are removed prior to calculation of LFP peak-to-peak amplitude (see “Methods” section). Similarly, thalamic electrical stimulation often evoked cortical spikes. As described in “Methods” section, any spikes that occurred within ± 1 ms of the electrical pulse were excluded from the analyses; similar time windows of exclusion were used for the 0 μA condition, enabling direct comparisons with trials in which current was actually injected.

With thalamic pulse trains, responses evoked by first and subsequent whisker deflections are smaller and more similar to one another than in the control condition (0 μA ; e.g., Fig. 2b).

This finding suggests that high frequency, high-intensity thalamic stimulation affects otherwise normally occurring sensory adaptation. In order to examine this further, we employed a more strongly adapting whisker stimulus, notably 20 Hz deflections (Khatri et al. 2004). With 20 Hz whisker deflections, alone peak-to-peak LFP amplitude decreases immediately after the first cycle and reaches a steady state of ~60% the initial value (Fig. 3a). With concurrent 400 μ A thalamic stimulation, which began 500 ms before the whisker deflection train, the LFP evoked by the first deflection is ~90% smaller than the control case, and there is little further reduction during the remaining whisker deflection cycles. Cycle-by-cycle amplitude sequences are shown in Fig. 3b for several values of current intensity. When whiskers are deflected alone (0 μ A), response amplitude during the second deflection is reduced on average by ~40%, and response amplitudes remain relatively stable for the remaining 39 cycles.

With increasing current intensity, overall LFP response amplitude decreases. First-cycle responses become progressively smaller with higher currents such that responses are more uniform across cycles with relatively little difference between first- and subsequent-cycle responses. Hence, as current intensity increases, the AI becomes larger, reflecting the fact that there is little or no change in responsiveness between first- and subsequent-cycle whisker deflections (Fig. 3c). Interestingly, the relation between adaptation and stimulus current is non-monotonic, initially decreasing and then increasing with larger currents. This can be understood upon closer inspection of the cycle-by-cycle amplitude sequences shown in Fig. 3b. Notably, first-cycle responses are largest in the control condition and only minimally reduced with 80 μ A pulses; the reduction of the later cycle responses is relatively large. With higher stimulus currents, responses to the first whisker deflection are already reduced such that with the largest currents, whisker-evoked responses are nearly constant throughout the 2 s of whisker deflections. With 80 μ A pulses, the electrical stimuli likely produce only mild cortical adaptation that is augmented by the whisker stimuli themselves. With larger currents, substantial adaptation has already occurred by the time the first whisker deflection is delivered; under these conditions, the whisker deflections themselves contribute little to the adaptation process.

Electrically induced LFPs in the layer IV barrel

In the previous section, we examined how a continuous, high frequency train of thalamic electrical impulses affects the whisker-evoked responses in layer IV. Multiple electrical pulses preceded each whisker deflection. Here, we examined the impact that a single electrical pulse has on the cortical response to a whisker deflection (Fig. 4). A single thalamic stimulus itself evokes a cortical response consisting of a short-latency negativity of 15–20 ms duration followed by a longer lasting positivity. When the whisker is deflected 10 ms after a 160 μ A electrical impulse, the short-latency negativity associated with the thalamic stimulation is followed by a second negativity beginning 6–7 ms after the whisker deflection (Fig. 4a, traces are offset for clarity). This second negativity is longer in duration, because thalamic activity evoked by a whisker stimulus is likely more temporally dispersed than activity evoked directly in the thalamus by an electrical pulse. Assuming that field potentials resulting from the whisker stimulation and the thalamic electrical stimulation superimpose linearly in the cortex, we subtracted the electrically induced LFP to estimate the contribution of the whisker-evoked response to the total signal. With this procedure, the negativity of the whisker-evoked LFP is seen to be reduced by ~25% as a result of the preceding thalamic stimulation (Fig. 4a, bottom). The subsequent positivity is also slightly reduced and delayed. Peak-to-peak amplitudes of the whisker-evoked component of the LFP become smaller with increasing electrical stimulation currents (Fig. 4b; $P < 0.05$; one-way ANOVA with Tukey's test). With higher currents, the whisker-evoked LFP is nearly abolished (Fig. 4c). The electrical pulses themselves evoked cortical responses that varied

from trial to trial. Figure 4d shows that some of the variability in whisker-evoked responses are likely due to variations in the efficacy of the immediately preceding electrical pulses. This relationship could reflect momentary, spontaneous changes in the excitability of the cortical circuitry or of the thalamic neurons themselves.

A whisker deflection can also reduce the amplitude of the response to a subsequent thalamic electrical stimulus. In order to examine this, we used an inter-stimulus interval of 20 ms, instead of 10 ms, so as to adjust for the slower time-course of the whisker-evoked response. Whisker deflection parameters were the same for all currents. As above, the LFP from whisker deflection alone was subtracted from the net LFP resulting from paired stimulation. When whisker stimulation precedes a 160 μ A thalamic pulse, the peak-to-peak amplitude of the electrically evoked LFP is reduced by 2.6 mV (~17%, Fig. 4e). Such small whisker-evoked reductions were observed for all current intensities, and there were no systematic differences in the magnitude of the effect.

Effects of thalamic pulse trains on thalamocortical transmission

Driving thalamocortical circuitry with periodic (100 Hz) electrical stimulation reduces whisker-evoked responses observed at the cortical level. Smaller cortical responses could reflect changes at the level of the cortex, or alternatively, a weaker incoming thalamic signal due to reduced excitability of thalamic neurons during a train of electrical pulses. Close inspection of electrically evoked LFPs suggests that they may have distinguishable pre- and post-synaptic components. Figure 5a shows an example LFP plotted at high temporal resolution. The waveform consists of an initial positive peak followed by a sharp negative transition and, less than a millisecond later, a second, smaller positive peak. A large amplitude, longer duration negativity ensues. The time course and overall shape of the waveform are remarkably similar, though considerably larger in amplitude, to that recorded in response to the spontaneous firing of single thalamocortical neurons (Swadlow and Gusev 2000; Bruno et al. 2003; Simons et al. 2007). With electrical stimulation, the earliest response component in the cortex occurs ~1 ms after pulse onset. This latency is consistent with a previously reported mean thalamocortical axon conduction time of 0.63 ms (Simons et al. 2007), and a “utilization” time of ~0.5 ms for the electrical pulse to evoke spikes in nearby thalamic neurons (Swadlow 1982). We assume that the earliest wave reflects the incoming thalamocortical volley and that its amplitude provides a measure of the synchronous firing of the presynaptic, thalamic neurons. By analogy with the axon terminal potential (AxTP) produced by a single thalamocortical spike (Swadlow and Gusev 2000), we use the term ‘population axon terminal potential’ (pAxTP) to refer to this early wave. Also by analogy with LFPs evoked by single thalamocortical neurons, we assume that the later waveform reflects the earliest post-synaptic response and use the term population synaptic negativity (pSN) to describe it. Figure 5b shows that the pAxTP but not the pSN persists following cortical synaptic inactivation with the glutamate receptor antagonist CNQX. These findings are consistent with similar, earlier work showing distinct pre- and post-synaptic components in cortical LFPs evoked by single thalamic neurons (Swadlow and Gusev 2000).

We examined pAxTPs and pSNs to determine whether they were both reduced in amplitude during trains of electrical pulses or whether pAxTPs remained constant while pSNs became smaller. The latter outcome would indicate that the incoming thalamocortical volley was unaffected and that smaller cortical LFPs reflect a diminished synaptic transmission and/or decreased excitability of the post-synaptic network. pAxTPs were quantified by the amplitude of the early biphasic wave, and pSNs were calculated as the area of the curve between the trailing pAxTP and the beginning of the following current pulse (Fig. 5a). Figure 5c plots the sequence of 300 pAxTP and pSN amplitudes during the entire 3 s of 100 Hz thalamic stimulation (320 μ A). Between 500 and 2500 ms, there was a concurrent 20 Hz

whisker stimulation, which resulted in small, yet distinct 20 Hz modulations of the pSN and pAxTP. Nevertheless, the overall slow time course of the (electrically evoked) pAxTP and pSN amplitudes is clearly visible. pAxTP amplitude remains relatively constant, while pSN amplitude steadily decrements, approaching a steady state near the end of the 3 s electrical stimulation period. The high amplitude of the pSN at the start of the electrical pulse train is consistent with the observation that some units displayed bursts of firing at this time (e.g., Fig. 1b, lower panel).

We quantified the adaptation observed in these electrically evoked LFP components by plotting the ratio of final, steady-state amplitude to the early peak amplitude (Fig. 5d). This measure is analogous to the AI used above to quantify the change in cortical unit and LFP responses to high-frequency whisker stimulation. As shown in Fig. 5d, the pAxTP is relatively insensitive to thalamic current intensity, whereas the pSN amplitude decreases with increasing current intensity. As a positive control, we applied electrical stimuli at high current (320 μ A) and at high frequency (300 Hz). This likely renders thalamic neurons at least partially refractory, diminishing the probability that any given neuron will fire a spike in responses to a single pulse. Consistent with this, we observed only a small pAxTP (Fig. 5a, lower trace). Thus, if 100 Hz trains substantially decreased thalamic firing, our pAxTP measure would have revealed it. Taken together, the findings suggest that the repeated, electrical stimulation of thalamocortical neurons adapts the layer IV postsynaptic response but has relatively little effect on the strength of the incoming thalamic volley.

Histology

We observed no obvious effect of the time elapsed from the first application of electrical stimulation during an individual experiment. This suggests that the viability of VPm neurons did not deteriorate during the course of an experiment. In some histological specimens, we observed a small zone of tissue damage surrounding the site of stimulation in VPm (Fig. 6). This likely reflects electrolytic microlesions produced by the current pulses, which in some cases were as high as 400 μ A. In order to ensure that damage to the thalamus did not by itself lead to smaller cortical responses, we performed one additional experiment wherein the 10 Hz whisker deflection/electrical stimulation protocol was presented only once; current intensities ranged from 0 to 120 μ A in steps of 40 μ A. Histology from this “low intensity” experiment revealed minimal damage in VPm (Fig. 6), comparable to what is typically observed with recording microelectrodes. Adaptation and attenuation effects were similar to those obtained at comparable current intensities in our other experiments (Fig. 2d, thick trace), indicating that electrically induced cortical effects are not merely a by-product of damage to VPm.

Discussion

We found that high-frequency electrical stimulation of VPm neurons causes an intensity-dependent decrease in the responses of cortical neurons to concurrent whisker deflection. Effects were evident both in population data, revealed by LFP recording and in single units. Electrical stimulation alone and whisker deflections alone both lead to decreased cortical responsiveness having a similar time course, and when the stimuli are combined, their effects appear to work in concert. These findings suggest that thalamic stimulation and ongoing peripheral sensory stimulation act through similar mechanisms to produce response attenuation, in the case of electrical stimulation, and sensory adaptation, in the case of whisker deflection. These mechanisms likely include history-dependent depression at thalamocortical synapses and engagement of inhibitory neurons within the cortical circuitry (Castro-Alamancos and Oldford 2002; Khatri et al. 2004). Inhibitory neurons in layer IV could also be excited by recurrent collaterals of corticothalamic neurons that are antidromically activated by the electric stimulation (Beierlein et al. 2003). The relative

contributions of each of these mechanisms may well depend on current intensity and frequency. Nevertheless, thalamocortical synaptic depression with or without strong local cortical inhibition will likely induce an effective “refractory” period during which subsequent stimuli, either current pulses or whisker deflections, evoke smaller responses. Electrical stimulation evokes highly synchronous thalamic firing and thus strong engagement of inhibitory as well as excitatory circuitry within the layer IV barrel. In this regard, it is not surprising that this manipulation produced more robust suppression of whisker-evoked responses than the converse (Pinto et al. 2003).

Our data indicate that thalamic stimulation induces its effects by acting at the level of the cortex, either at the thalamocortical synapse and/or in post-synaptic cortical circuitry. Notably, our, albeit indirect, measure of thalamic population firing, evidenced by the pAxTP, indicates that VPM neurons continue tracking electrical stimuli up to at least 100 Hz. Despite the high thalamocortical firing rates likely induced by the current, the steady-state post-synaptic cortical response is small. The suppressing effects of thalamic stimulation are likely to be frequency dependent. With relatively low frequencies (e.g., 20–50 Hz), electrical stimulation likely preserves signal transmission, as we observed for low-intensity currents. On the other hand, even higher frequency stimulation than the 100 Hz pulses used here could lead to substantially smaller cortical responses because of reduced thalamic firing itself. We found that the pAxTP is smaller with delivery of 300 Hz current, indicating a reduction in the afferent signal. This probably reflects a greater likelihood that an individual thalamic neuron is in a refractory state at any given moment.

Repetitive whisker deflections at >10 Hz produce response adaptation in subcortical structures at different levels in the whisker barrel afferent pathway including: the trigeminal ganglion (Fraser et al. 2006), the trigeminal nucleus (Hirata et al. 2009), and the thalamus (Khatri et al. 2004; Temereanca et al. 2008). Our electrical stimulation targeted the thalamus and thus likely does not affect whisker-evoked responses upstream in the afferent pathway (trigeminal ganglion and nucleus). There is, however, the possibility that thalamic stimulation antidromically activates second-order neurons in principal sensory nucleus (PrV) and suppresses their spiking due to the high frequency nature of the stimulus. It has been shown recently, however, that electrical stimulation of the medial lemniscus evokes equivalent responses in VPM, either with or without local inactivation of PrV (Lee et al. 2008); thus negating the effect of potential antidromically activated spikes in PrV on feedforward transmission of whisker signals. This leads us to believe that the effects of electrical stimulation in the thalamus affect sensory transmission only in the feedforward direction, at least up to the highest currents that we used. Another possibility is that thalamic stimulation recruits additional local inhibition in the thalamus, thus making it more difficult for incoming whisker-evoked signals to evoke a thalamic response. We deem this unlikely, however, as it was recently shown that cortical adaptation is unaffected by the level of local inhibition in VPM (Hirata et al. 2009).

We chose 100 Hz stimulation because it is within the range of frequencies often used for DBS in clinical applications (Perlmutter and Mink 2006). We found that at high intensities cortical responses were markedly reduced or abolished altogether. Such effects are consistent with the seemingly paradoxical finding that electrical stimulation of a pre-synaptic population of excitatory projection neurons can have the same effect as a surgical lesion (McIntyre et al. 2004b). Conceivably, lower intensity/frequency stimulation could improve signal processing by acting through feedforward mechanisms that normally enhance response specificity (Khatri et al. 2004; Hirata and Castro-Alamancos 2006) or by restoring levels of post-synaptic activity that may be abnormally elevated (Simons and Land 1987).

The thalamocortical projection is characterized by a high degree of convergence (Bruno and Simons 2002; Bruno and Sakmann 2006). It is therefore possible that VPm neurons that continue to convey the whisker-evoked signal are not necessarily the same cells that are activated by the current, that is, the whisker-signal conveying thalamic neurons could be located distant from the stimulation electrode. Higher intensity thalamocortical stimulation could more effectively suppress cortical responses due to greater stimulus spread (McIntyre et al. 2004a). Issues of spatial specificity could conceivably be addressed by applying current in one barreloid (e.g., D2) and stimulating an adjacent whisker (e.g., D1) while recording in that whisker's cortical barrel.

Interestingly, at all but the highest stimulation currents, concurrent whisker deflections were able to evoke cortical responses. Although we were unable to monitor VPm spiking during the current pulses, our finding that cortical neurons continued to respond to whisker deflection indicates that thalamic neurons were being activated by trigeminothalamic inputs during thalamic stimulation. VPm neurons are strongly driven by whisker-evoked trigeminothalamic inputs, enabling them to fire in response to high frequency whisker deflections (Deschenes et al. 2003). Because of such efficacious afferent drive, an individual thalamocortical neuron could conceivably follow the whisker stimuli in addition to the thalamic electrical stimulation. In brain, areas where afferent drive may be less effective, ongoing electrical stimulation, even at low currents, may substantially impede signal transmission.

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Fig. 1.

Simultaneous whisker deflections and thalamic high frequency electrical stimulation. **a** Periodic whisker stimuli (*top*) consisted of brief whisker deflections of 0.7 mm amplitude with rise and decay times of 5 ms each, delivered at either 50 or 100 ms intervals. Biphasic electrical pulses (0.4 ms each phase) were synchronized with the 10 or 20 Hz whisker deflections (*bottom*). **b** Raster plots of a sample cortical unit activity with concurrent electrical thalamic stimulation and whisker deflection. Each trial of the stimulation protocol consisted of 3 s of electrical stimulation with concurrent 10 Hz periodic whisker stimulation between 0.5 and 2.5 s (*shaded area*). Occasionally, transient increases in cortical activity were observed at the beginning of each trial (see text)

Fig. 2.

Effects of combined whisker deflection and electrical stimulation in the thalamus. **a** PSTHs for a sample layer IV neuron without thalamic stimulation (*top*) and 320 μA current stimulation (*bottom*). Stars indicate times of whisker deflection. **b** Population peristimulus histograms showing transient responses of 22 layer IV neurons to 10 Hz whisker deflections in control (0 μA , *top*) and electrically stimulated (160 μA , *middle*) conditions. Thick lines: 1st cycle response; thin lines; cycles 11–20. Error bars indicate s.e.m. The ratio of first cycle PSTH to late cycle averaged PSTHs for the control case (*thick line; bottom*) peaks at larger values, ~ 6 , during the early phase of the whisker response, as compared to the electrically stimulated case (*thin line*). **c** LFPs evoked by whisker deflection during on-going thalamic stimulation. First-cycle responses are shown for several different current intensities. **d** Mean spike counts per cycle, averaged over all whisker cycles (*open circles*; $n = 22$; $*P < 0.05$, *top row*), and LFP peak-to-peak amplitude averaged over all whisker cycles (*filled circles*; $n = 3$) in response to 10 Hz deflections for different thalamic stimulus current intensities. LFP data from the low current experiment (*thick solid line*; $n = 3$; $*P < 0.05$, *bottom row*) are consistent with results from experiments using the standard protocol (see “Methods” section). Error bars indicated s.e.m

Fig. 3.

Thalamic electrical stimulation and thalamocortical adaptation. **a** An example trial-averaged LFP evoked by 20 Hz whisker deflections with 0 μA (*solid line*) and 400 μA (*dashed line*) electrical stimulation. *Asterisks* indicate whisker deflections times. **b** LFP amplitude as a function of stimulus cycle for different current intensities ($n = 3$). **c** LFP adaptation index as a function of thalamic current. Whiskers were deflected at 20 Hz. Indices were computed using an average of the last 10 deflections

Fig. 4.

Suppressive interactions of whisker deflections and electrical stimulation. **a** An electrical pulse delivered in the thalamus (160 μA) causes a short-latency negativity in the extracellular potential followed by a broader, shallower positivity (*top panel*). When the same electrical impulse is followed by a whisker deflection (10 ms later), there is a second pronounced negativity that is more temporally dispersed (*middle panel*). When the electrical stimulation-alone LFP is subtracted from the LFP resulting from combined stimulation, the resulting LFP contribution from whisker stimulation (*gray line, bottom panel*) is reduced in amplitude relative to the LFP from the same whisker deflection without electrical stimulation (*dashed line*). *Open circles* indicate electrical impulse times and *closed circles* indicate whisker deflection onset times. **b** The amplitude of the whisker-evoked component of the LFP is reduced with increasing current intensity (shown for three different current intensities). **c** Trial averaged mean whisker-evoked LFP amplitudes are plotted as a function of current intensity. **d** The trial-by-trial amplitudes of the whisker-evoked component of the LFP are plotted against the corresponding amplitude of the initial component of the LFP from thalamic stimulation for all currents from 80 to 400 μA . The best fit line for all amplitude pairs shows an inverse proportionality on a trial-by-trial basis ($R = -0.6657$). **e** When whisker deflection (time 0) precedes the current pulse by 20 ms, the amplitude of the current-induced LFP component is reduced (*dash*) though not to the same extent as the electrically induced suppression of the whisker-evoked component. *Error bars* indicate 1 SD. Mean values were calculated as an average of 280 single deflection responses

Fig. 5.

Pre- and post-synaptic components of electrically evoked LFP. **a** An example layer IV LFP evoked by a single thalamic current pulse from a 100 Hz train (320 μ A). Early and late components are identified as pAxTP (arrowheads) and pSN (see text). pSN is quantified by amplitude measured from a straight line joining the second positivity of the pAxTP and the beginning of the next electrical stimulus cycle. Lower trace shows LFP for one cycle of a 300 Hz current pulse train. The pAxTP is greatly diminished. **b** pSN but not pAxTP is abolished by CNQX (current intensity: 160 μ A). **c** pAxTP (dashed line) and pSN (solid line) amplitudes during a 3-s trial of combined electrical stimulation (240 μ A) and 20 Hz periodic whisker deflection. **d** Ratio of pAxTP or pSN final amplitude to the largest amplitude during the 3-s trial as a function of electrical stimulus intensity. Mean values were calculated as an average of 3000 single electrical impulse responses

Fig. 6.

Thalamic stimulation and tissue damage. 80 μm section through VPm showing a microlesion at a stimulation site from an experiment in which multiple (>4) presentations of the full series of thalamic stimuli were used (Left); current intensities ranged from 0 to 400 μA . A section from an experiment where few stimulation protocols were delivered and currents did not exceed 120 μA (Right). The electrode track is visible but there is no microlesion