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Cellular Mechanisms of the Augmenting Response: Short-Term Plasticity in a Thalamocortical Pathway

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Some thalamocortical pathways display an "augmenting response" when stimuli are delivered at frequencies between 7 and 14 Hz. Cortical responses to the first three stimuli of a series increase progressively in amplitude and are relatively stable thereafter. We have investigated the cellular mechanisms of the augmenting response using extracellular and intracellular recordings *in vivo* and in slices of the sensorimotor neocortex of the rat.

Single stimuli to the ventrolateral (VL) nucleus of the thalamus generate EPSPs followed by feedforward IPSPs that hyperpolarize cells in layer V. A long-latency depolarization interrupts the IPSP with a peak at ~200 msec. A second VL stimulus delivered during the hyperpolarization and before the peak of the long-latency depolarization yields an augmenting response. The shortest latency for augmenting responses occurs in cells of layer V, and they appear in dendrites and somata recorded in upper layers ~5 msec later. Recordings *in vitro* show that some layer V cells have hyperpolarization-activated and deinactivated conductances that may serve to increase their excitability after IPSPs. Also *in vitro*, cells from layer V, but not from layer III, generated augmenting responses at the same stimulation frequencies that were effective *in vivo*. Control experiments indicated that neither paired-pulse depression of IPSPs nor presynaptically mediated facilitation can account for the augmenting response. Active dendritic conductances contribute to the spread of augmenting responses into upper layers by way of back-propagating fast spikes, which attenuate with repetition, and long-lasting spikes, which enhance in parallel with the augmenting response. In conclusion, we propose that the initiation of augmenting responses depends on an interaction between inhibition, intrinsic membrane properties, and synaptic interconnections of layer V pyramidal neurons.

Key words: thalamus; neocortex; dendrite; short-term plasticity; voltage-dependent conductances; synchronization; layer V pyramidal cell

The "augmenting response" is a progressive enhancement of thalamocortical-evoked potentials that occurs during low-frequency stimulation (Dempsey and Morison, 1943). The augmenting response is readily differentiated from other types of responses induced in the cortex by thalamic stimulation. The "primary response," for example, is the short-latency cortical effect of stimulating specific thalamocortical afferents, and it is depressed at stimulus frequencies optimal for the augmenting response (Castro-Alamancos and Connors, 1996b). The laminar profile of the "recruiting response" (i.e., surface-negative and middle layer-positive) is different from that of the augmenting response (i.e., surface-positive and middle layer-negative) and is believed to arise from the dense and widespread projections of some thalamic nuclei (e.g., ventromedial nucleus) to layer I (Purpura and Shofer, 1964; Glenn et al., 1982; Herkenham, 1986).

Despite a long history of research (Spencer and Brookhart, 1961; Purpura and Shofer, 1964; Sasaki et al., 1970), the mechanisms of the augmenting response are still obscure. Morison and Dempsey (1943) originally suggested a thalamic origin; however, Morin and Steriade (1981) proposed that the augmenting response arises from the intrinsic organization of the cerebral cortex and may be independent of thalamic mechanisms. Ferster and Lindstrom (1985a) concluded that the augmenting response in visual cortex depends on the frequency-dependent properties of the intracortical axon collaterals of antidromically activated corticothalamic neurons (i.e., layer VI cells that project to layer IV). More recently, Metherate and Ashe (1994) proposed that a phenomenon similar to the augmenting response, recorded in auditory cortex, arises when frequency-dependent depression of IPSPs leads to the facilitation of NMDA receptor-mediated EPSPs. In general, there is agreement that the augmenting response does not require the thalamus (however, see Mishima and Ohta, 1992), but its cellular mechanisms are in dispute.

In recent studies of the sensorimotor cortex of rats, we concluded that the thalamus is not necessary for generating the augmenting response, that NMDA receptors are not involved, and that layer V (specifically its pyramidal cells) initiates the augmenting response (Castro-Alamancos and Connors, 1996b,c). Here we describe investigations of the cellular mechanisms underlying the augmenting response. The results indicate that activity in thalamic afferents projecting to layer V initiates a sequence of synaptic and intrinsic membrane-dependent events that serve to prime the cortical network; subsequent afferent activity, triggered within the proper interval, evokes an augmented response because of heightened neuronal excitability in layer V. The spread of the augmenting response to upper cortical layers depends on both synaptic interconnections and active dendritic conductances.

MATERIALS AND METHODS

Experiments were performed both *in vivo* and in slices maintained *in vitro*. The methods used for whole-animal recording have been described previously (Castro-Alamancos and Connors, 1996b,c). Briefly, Sprague

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Dawley rats (250–350 gm) were anesthetized with ketamine HCl (100 mg/kg, i.p.) and supplemented regularly (50 mg/kg, i.m.). After induction of surgical anesthesia, the animal was placed in a stereotaxic frame. All skin incisions and frame contacts with the skin were injected with lidocaine (2%). A unilateral craniotomy extended over a large area of the parietofrontal cortex. Small incisions were made in the dura as necessary, at the locations of insertion of the stimulating and recording electrodes. The cortical surface was covered with saline for the duration of the experiment. Body temperature was monitored and maintained constant with a heating pad (36–37°C). All surgical procedures were reviewed and approved by the Institutional Animal Care and Use Committee of Brown University.

Thalamic-stimulating electrodes were inserted stereotactically (all coordinates are given in millimeters and refer to bregma and the dura according to the atlas of Paxinos and Watson, 1982). Coordinates for the ventrolateral (VL) nucleus were approximately anterior-posterior = −2.0, lateral = 2.0, and depth = 5.5. Stimulus current intensity was selected to induce a stable response (<200 μA), and stimuli were monophasic and 200 μsec in duration. Insulated, twisted, bipolar stainless steel electrodes were used for stimulation. Recording electrodes were Teflon-insulated platinum-iridium wires (0.007 inch diameter, 0.005 inch tip size). Intracellular (conventional sharp-type) recording electrodes were filled with 3 M potassium acetate (80–120 MΩ), and recordings were made from cells of different cortical layers. At the end of each experiment, electrolytic marking lesions were placed at the thalamic locations that had served as stimulation sites. The animals were given an overdose of sodium pentobarbital and decapitated, and the brain was extracted and placed in fixative solution (5% paraformaldehyde in saline). Sections of the frontoparietal cortex and thalamus were cut with a vibratome and stained for Nissl.

Methods for preparing and recording from slices of sensorimotor cortex have been described previously in detail (Castro-Alamancos et al., 1995, 1996a). The regions of cortex used *in vitro* were the same as those studied *in vivo*. In the slice, stimulation (400–800 μm from cell body) was applied within layers III–V or, in a few cases, the white matter. The intracellular recordings that were selected for analyses had overshooting action potentials and stable membrane potentials more negative than −60 mV for at least 15 min. Recordings were identified as regular-spiking cells, intrinsically bursting cells, or dendritic impalements by applying current pulses of different intensities (Connors and Gutnick, 1990). In the case of dendritic impalements, action potentials were of low amplitude (<50 mV) and displayed waveform characteristics similar to morphologically confirmed dendritic impalements (Amitai et al., 1993; Kim and Connors, 1993; Stuart and Sakmann, 1994).

Electrophysiological responses were sampled at 10 KHz and stored and analyzed on a computer using Experimenter's Workbench (Data Wave Technologies) and Origin (Microcal Software) software.

RESULTS

Extracellular and intracellular correlates of the augmenting response *in vivo*

Extracellular field potential recordings were used to locate the region of maximal VL-evoked augmenting responses in the primary motor cortex of anesthetized rats (Castro-Alamancos and Connors, 1996b). Intracellular recordings were then obtained from different layers in the same region of cortex. The depth of the recording electrode relative to the pia was noted as an indication of the layer in which recorded cells were located. The sample included regular-spiking cells ($n = 33$), intrinsically bursting cells ($n = 7$) (Connors and Gutnick, 1990), and apparent intradendritic recordings ($n = 5$) (Kim and Connors, 1993). Regular-spiking cells were recorded in layers II through VI, whereas bursting cells were found only around layer V (i.e., 1000–1500 μm below the pia). Dendritic recordings were obtained only from the upper layers (i.e., 300–800 μm).

A single stimulus to VL triggers a characteristic sequence of responses recorded intracellularly: an initial fast EPSP is terminated sharply by a strong, hyperpolarizing IPSP that lasts for ~400-500 msec (Fig. 1*A*); the IPSP is interrupted by a long-latency depolarizing potential that peaks at ~200 msec (Fig. 1*A*, *asterisk*). A second VL stimulus delivered during the IPSP and before the peak of the long-latency depolarization triggers an EPSP, which is augmented compared with the first, and evokes one or more action potentials (Fig. 1*B*); however, when the second stimulus is delivered at the peak of the long-latency potential (e.g., 200 msec) or subsequently (e.g., 300 msec), the response is not augmented (Fig. 1*C*). The augmenting response increases incrementally with repetitive stimulation. Figure 1*D* shows it increasing in amplitude during the first three responses of a 10 Hz stimulus train, after which it reached a stable size. The long-latency potentials always follow the last stimulus by ~175-200 msec (Figs. 1*B*, *asterisk*, 3).

Figure 1*C,D* illustrates simultaneous intracellular events and field potentials, in particular the correspondence between the long-latency depolarization in single neurons and the late, slow negativity recorded extracellularly in layer V. Figure 2*A* shows the close relationship between the peak of the long-latency field potential (*bars*) and the termination of the augmenting response interval (*circles*; $n = 10$ animals). Thus, the strength of the augmenting responses increased progressively between 50 and 150 msec but was abruptly inactivated at the peak of the long-latency potential.

The augmenting response *in vivo* originates in layer V cells

The profile of extracellular currents revealed by current-source density analysis has indicated a central role for layer V cells in the initiation of the augmenting response (Castro-Alamancos and Connors, 1996b,c). We compared intracellular and extracellular recordings to chart the flow of augmenting activity in more detail. Field potentials in the primary motor cortex during VL stimulation revealed that the shortest latency of the augmenting response is in layer V (between 1000 and 1500 μm) (Fig. 2*B*). Latencies are significantly longer in the upper layers. For example, the augmenting response recorded at a depth of 500 μm begins ~5 msec after that at 1500 μm (Fig. 2*B*). All neurons recorded *in vivo* ($n = 45$) displayed an augmenting response when VL was activated at the appropriate interstimulus intervals; however, the latencies to the augmenting responses varied with the recording depth of the neuron. Comparisons of sequentially recorded (i.e., in the same electrode penetration) intrasomatic, intradendritic, and extracellular potentials reinforced the conclusion that the augmenting response is initiated in layer V (Fig. 3). Thus, somatic recordings of augmenting responses from layer V cells (1000–1500 μm depth) were phase-locked to the shortest latency component of the concurrently recorded field potential from layer V (Figs. 2*B*, 3). Neurons from upper layers (300–1000 μm depth) displayed augmented potentials, but the average latency of the upper layer cells was 5 msec longer than that of the cells in layer V (Figs. 2*B*, 3). Intradendritic recordings of augmenting responses obtained within layer III were phase-locked with the peak extracellular negativities recorded within that layer and coincident with augmenting responses from somatic recordings in layer III (Fig. 2*B*). In addition, the long-latency field potentials and their associated neuronal depolarizations (175–200 msec) occurred in layer V (Fig. 3). In summary, both extracellular and intracellular recordings indicate that the augmenting response originates within layer V and spreads into the upper layers during the next 5 msec.

Voltage-dependent membrane properties of layer V cells and augmenting responses *in vitro*

The recordings from layer V cells *in vivo* suggested that the VL-evoked IPSP is important to the generation of the augmenting

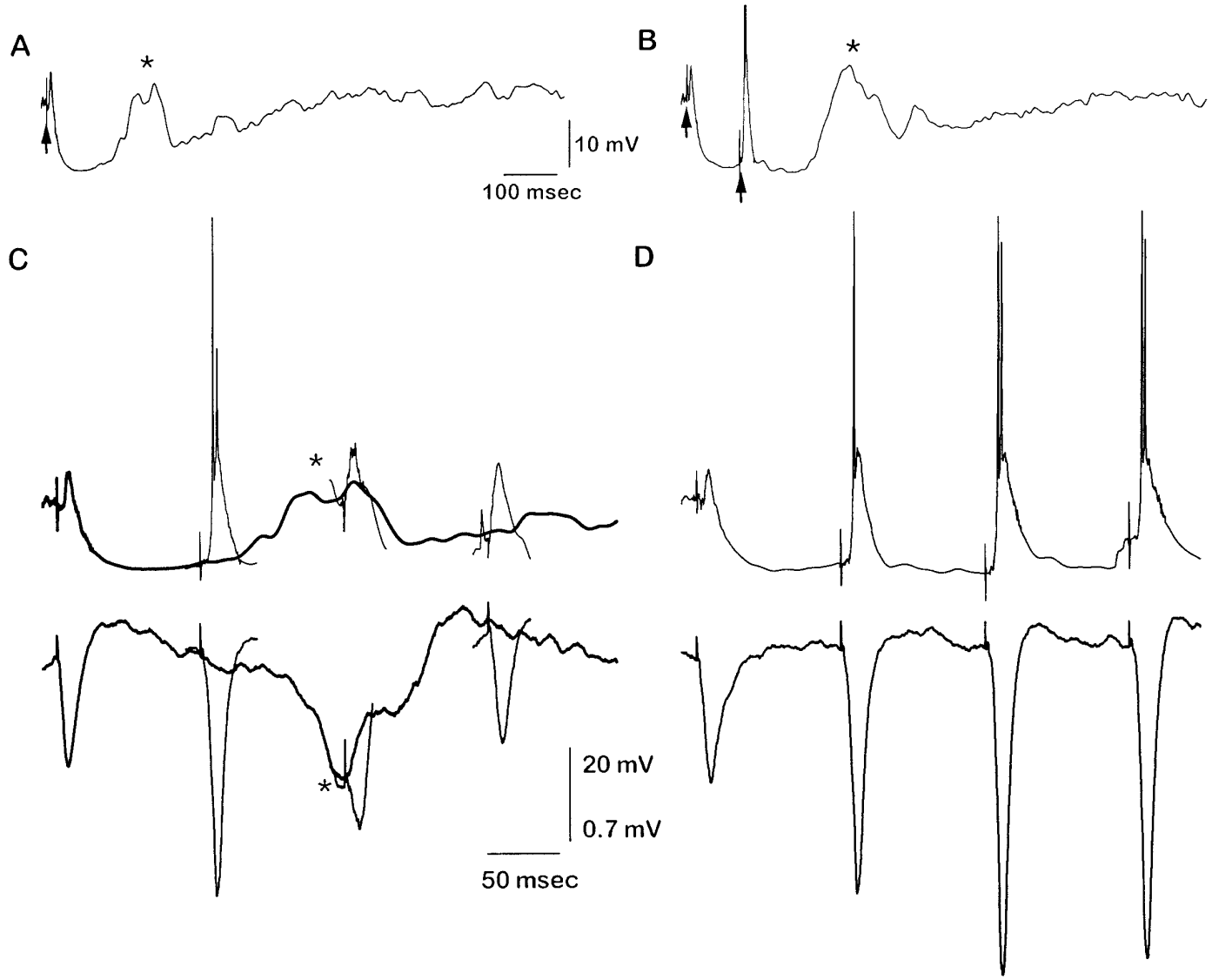

Figure 1. Extracellular and intracellular measurements of the augmenting response *in vivo*. *A*, Intracellular recording from a layer V cell of the sensorimotor cortex in response to one stimulus delivered to VL (*arrow*). A short-latency EPSP was followed by a sharp IPSP, which was then interrupted by a long-latency depolarization (*asterisk*). *B*, A second VL stimulus delivered after 100 msec produced an augmented response that triggered two action potentials (truncated); the long-latency depolarization (*asterisk*) followed. *C*, Simultaneous intracellular (layer V cell) and extracellular recordings (1000 μm in depth) during VL stimuli. Paired stimuli were delivered at different intervals (100, 200, and 300 msec). An augmenting response was triggered when the second stimulus was delivered during the hyperpolarization preceding the long-latency potential (*asterisk*); responses at longer intervals were not augmented. *D*, Four pulses delivered at 10 Hz show the incremental nature of the augmenting response, which enhanced after the first three stimuli and reached a steady state by the third pulse.

response, because the effective intervals of augmenting parallel the time course of the IPSP before the long-latency potential. We hypothesized that voltage-dependent membrane currents of layer V cells might be activated or deinactivated by the hyperpolarization of the IPSP, thus enhancing the excitability of the cells (Castro-Alamancos and Connors, 1996b). Neurons (n = 50) recorded intracellularly from layer V of slices *in vitro* produced various intrinsic firing patterns (Agmon and Connors, 1989; Connors and Gutnick, 1990; Silva et al., 1991): regular-spiking cells with various rates of adaptation (n = 19), cells capable of repetitive intrinsic bursting (n = 10), and cells that burst nonrepetitively or generated nonadapting trains of single spikes (n = 21). In response to long depolarizing stimuli, repetitively bursting cells fired bursts at frequencies similar to those that generate augmenting responses (i.e., 7–14 Hz) (Fig. 4*A*). Long hyperpolarizing stimuli of these cells produced a voltage deflection that peaked at ~75 msec and then sagged to a stable, less hyperpolarized level at ~200 msec; similar behavior has been attributed to a hyperpolarization-activated cation current (Wang and McCormick, 1993). At the offset of hyperpolarization, such cells generated rebound depolarizations that could be big enough to generate bursts (Fig. 4*A*); similar behavior has been attributed to a low-threshold calcium current (Jahnsen and Llinas, 1984; Friedman and Gutnick, 1987). The hyperpolarizing sags and rebound depolarizations were observed in all repetitively bursting cells, where they were especially prominent, but they also occurred to different extents in other cell types. The nonrepetitively bursting cells and cells with nonadapting single spiking all displayed clear

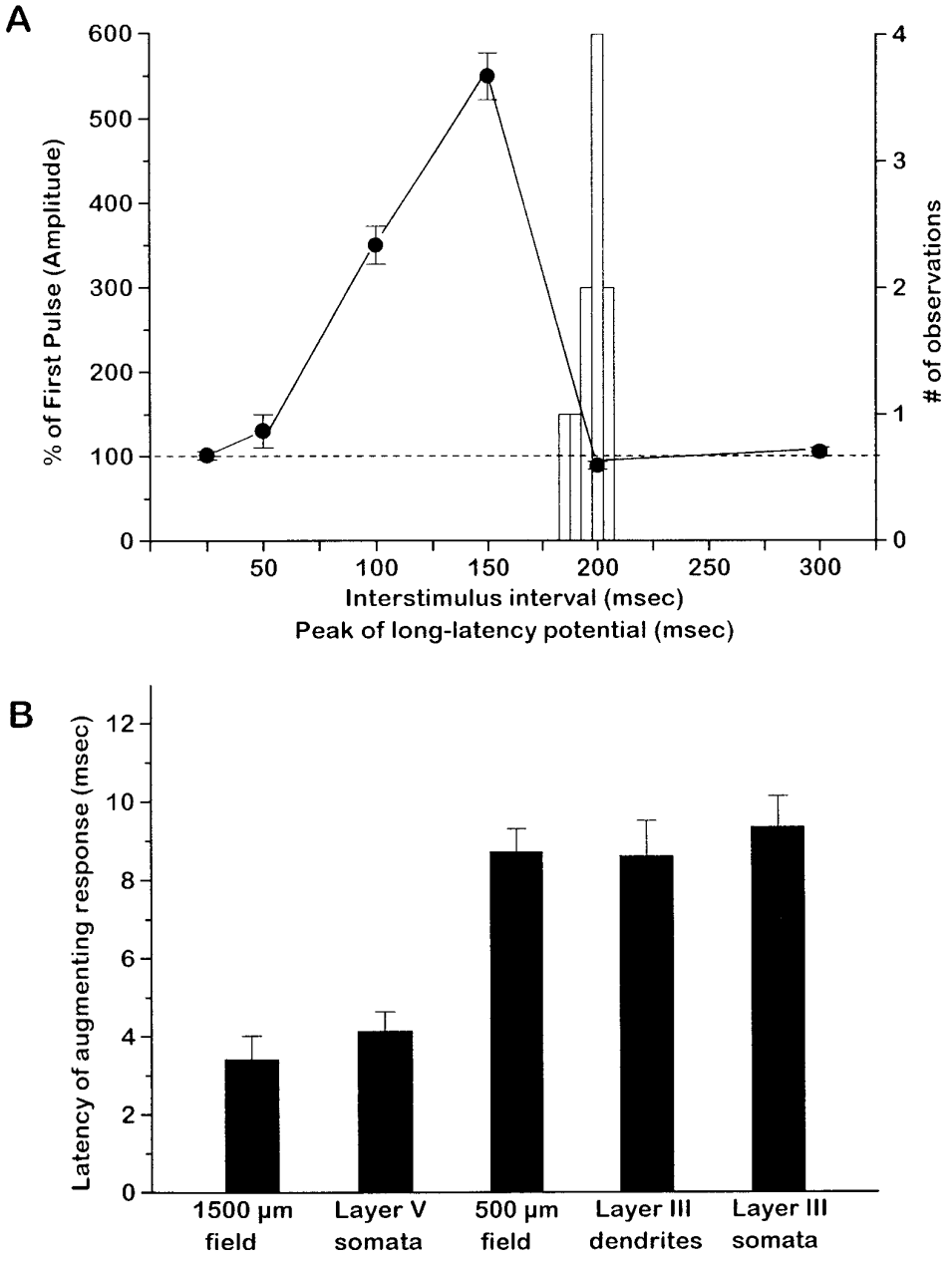

Figure 2. The augmenting response *in vivo* occurs within a narrow range of interstimulus intervals and is initiated in layer V. *A*, Effect of paired-pulse VL stimulation as a function of interstimulus interval (*circles* and *left y*-axis; amplitude of second response as percentage of the first), and timing of the peak of the long-latency potential for 10 cases (*bars* and *right y*-axis). Note that the augmenting response begins at an interstimulus interval of 50 msec and is abolished at the peak of the long-latency potential (200 msec). *B*, Latency of the augmenting response (i.e., the start of the response to the second stimulus delivered at a 100 msec interstimulus interval in VL) when recorded extracellularly in layer V (1500 μm deep; n = 5), intracellularly from neuron somas in layer V (1000–1500 μm; n = 5), extracellularly from layer III (500 μm deep; n = 5), intracellularly from dendrites located in the upper layers (layer III dendrites; n = 5), or from somas in the upper layers (n = 5 layer III somas; 300–1000 μm). The shortest latencies were observed in cells located in layer V. All data expressed as mean ± SEM.

evidence of rebound depolarizations and little or no evidence of hyperpolarizing sags. Only adapting, regular-spiking cells did not produce sags or rebound depolarizations. This indicates that specific populations of layer V neurons possess inward currents that are either activated or primed by membrane hyperpolarization. We have never observed such membrane properties in neurons of the upper layer cells *in vitro* (Castro-Alamancos et al., 1995; Castro-Alamancos and Connors, 1996a).

When stimulated synaptically, layer V cells in the slice generated a small initial EPSP followed by a strong biphasic IPSP, which hyperpolarized cells when their membrane potentials were set to approximately −60 to −65 mV with steady injected current (Fig. 5*A*). A second stimulus delivered during the hyperpolarization elicited an augmented response (Fig. 5*A*). The most effective intervals for augmenting in the slice were between 50 and 200 msec (Figs. 5*A*, 6), as they were *in vivo*. Augmented responses could be induced in all cells recorded in layer V that were tested (n = 15) but in none of the layer III cells (n = 25). During repetitive stimulation, the *in vitro* augmenting response also increased incrementally (Fig. 5*B*), as it does *in vivo* (Figs. 1*D*, 3). In clear contrast, the regular-spiking cells in layer III of the slice did not generate augmenting responses during paired stimuli (n = 25 cells) (Fig. 5*C*). Instead, layer III cells produced paired-pulse depression over a wide range of interstimulus intervals (Fig. 6, *open circles*). These results were observed with both methods of stimulation used in the slice, i.e., intracortical and white matter stimulation.

To test the frequency sensitivity of synaptic inhibition, recordings were made from cells of layers V and III in the presence of the glutamate receptor antagonists AP5 and CNQX to block all EPSPs (for details, see Castro-Alamancos and Connors, 1996a). The IPSPs thus isolated displayed paired-pulse depression over a wide range of interstimulus intervals (Fig. 6, *squares*). Thus, the frequency sensitivity of inhibition cannot by itself account for the

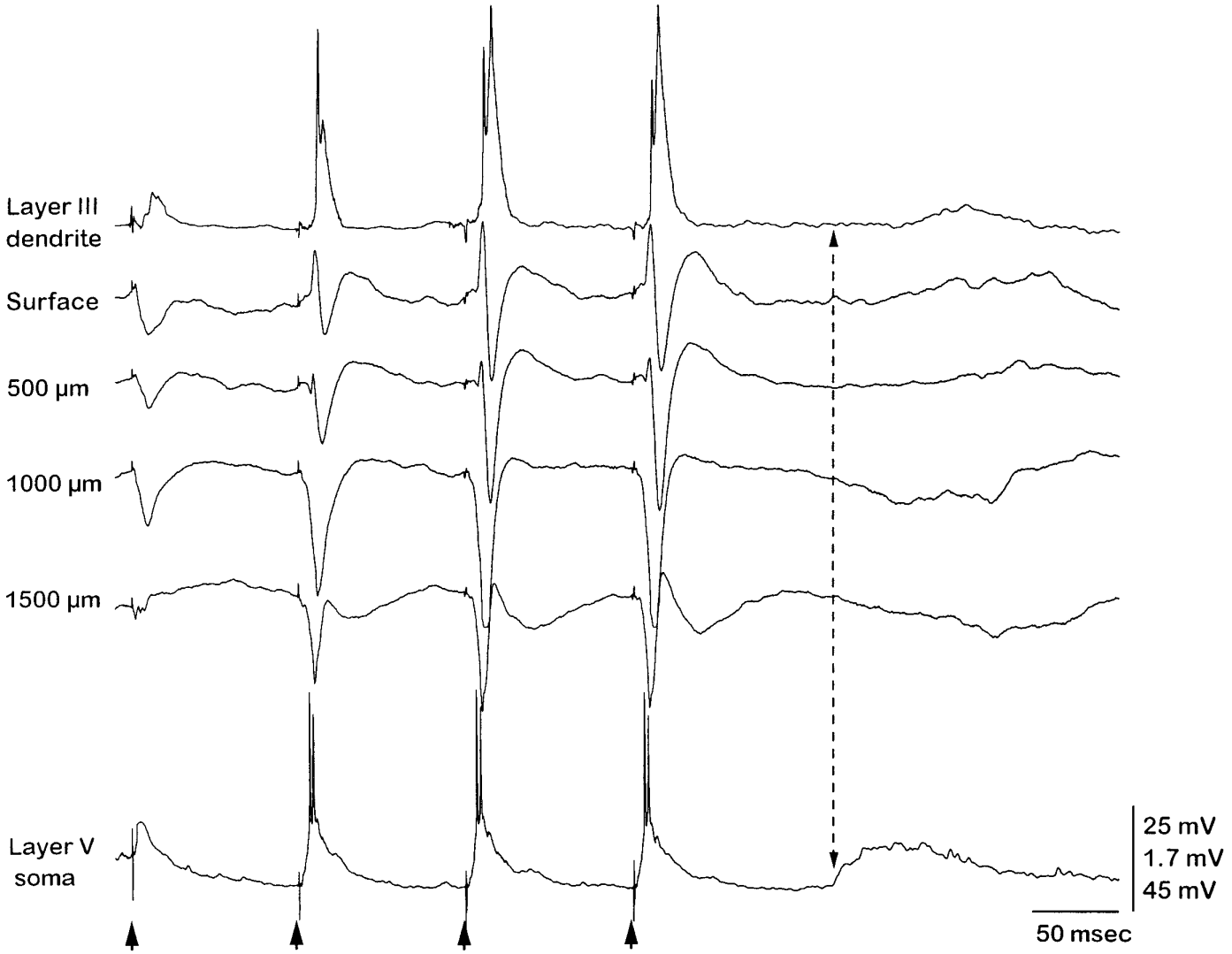

Figure 3. Comparison of sequentially recorded intrasomatic, intradendritic, and extracellular potentials indicate that the augmenting response is initiated in layer V. Recordings were made along a single electrode track as trains of four stimuli (*arrows*) were delivered to VL at 10 Hz. Intracellular recordings were from a dendrite located in layer III (400 μm deep; *top trace*) and a soma in layer V of an intrinsically bursting cell (1400 μm deep; *bottom trace*). The *middle traces* show extracellular field potentials at various depths in the cortex (surface, 500, 1000, and 1500 μm). Note that the somatic layer V recording was phase-locked to the shortest latency component of the concurrently recorded field potential from layer V, whereas the upper layer dendrite was phase-locked to the longer-latency negativities in those layers. The long-latency depolarization, ~175-200 msec after the last stimulus, occurred first in the layer V cell (*dashed line* with *arrows*).

strong augmenting responses observed in drug-free layer V cells at intervals between 50 and 200 msec *in vitro* (Fig. 6, *filled circles*), because depression of IPSPs extended to much longer intervals (>500 msec) and was actually strongest at shorter intervals (i.e., 25 msec) (Fig. 6), when there are no augmenting responses.

A primary instigator of the augmenting response could be either frequency-sensitive facilitation of excitatory synapses or a change in intrinsic membrane excitability triggered by IPSP-induced hyperpolarization. Paired-pulse facilitation is usually generated by presynaptic mechanisms (Zucker, 1989). If postsynaptic properties are of primary importance in generating the augmenting response, then it should be possible to induce an augmenting response by priming a layer V cell with a single shock to an IPSP-producing pathway and testing with a second, independent excitatory pathway onto the same cell. We placed two stimulating electrodes on opposite sides of an intracellularly recorded layer V cell, so that each activated an independent horizontal pathway (Fig. 7*A*, *S1* and *S2*) (independence was tested by showing that the responses summed linearly) and stimulated them in different sequences. A stimulus to either pathway was capable of priming the response to the other pathway, with an augmenting response resulting. Paired stimulation of S2 at an interval of 100 msec generated an augmenting response, as usual (Fig. 7*B*). When a shock to S1 was substituted as the first (priming) stimulus, the response to an S2 stimulus was also strongly augmented. This result suggests that presynaptic mechanisms are unlikely to be of primary importance in the mechanisms of initiation of the augmenting response.

Intradendritic recordings during augmenting responses *in vivo* and *in vitro*

Some intracellular recordings obtained *in vivo* ($n = 5$) (Fig. 8) or in slices ($n = 10$) (Fig. 9) displayed the electrophysiological characteristics of intradendritic recordings. Despite large, stable

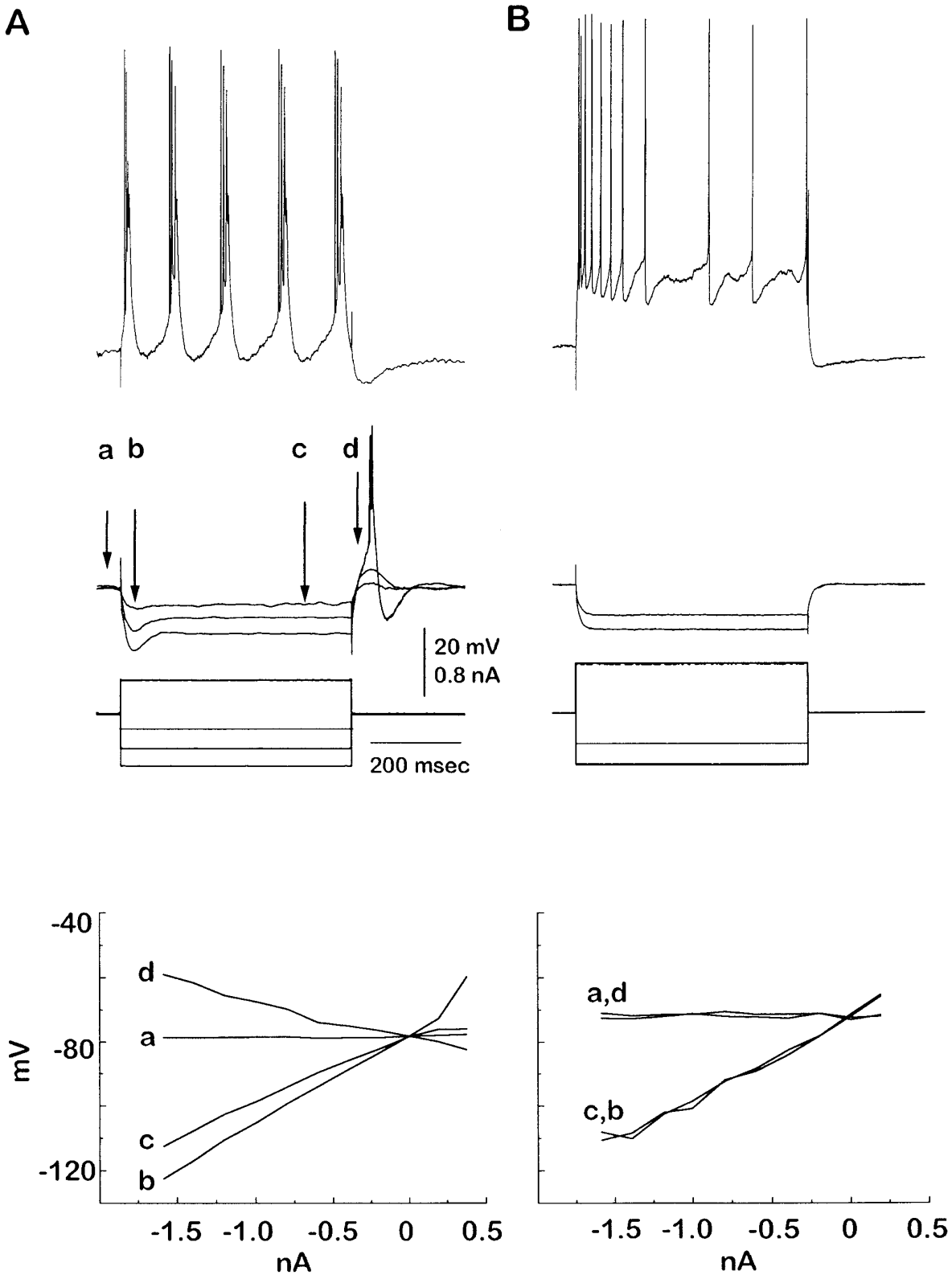

Figure 4. Intrinsic membrane properties of layer V cells in slices *in vitro*. *A*, Repetitively bursting cells in layer V fire bursts within the frequency range of augmenting responses (*top*). During negative intracellular current injections, they show voltage sags characteristic of hyperpolarization-activated currents (such as I_H, *middle*). After negative pulses, they generate rebound depolarizations typical of cells with low-threshold calcium currents (I_T). Spikes during the rebound burst are truncated. The *graph* (*bottom*) plots the current–voltage relationship of the bursting cell, as measured at the points indicated (*a–d*). *B*, Adapting regular-spiking cells in layer V show no evidence of hyperpolarization-activated currents. Traces and graph as in *A*.

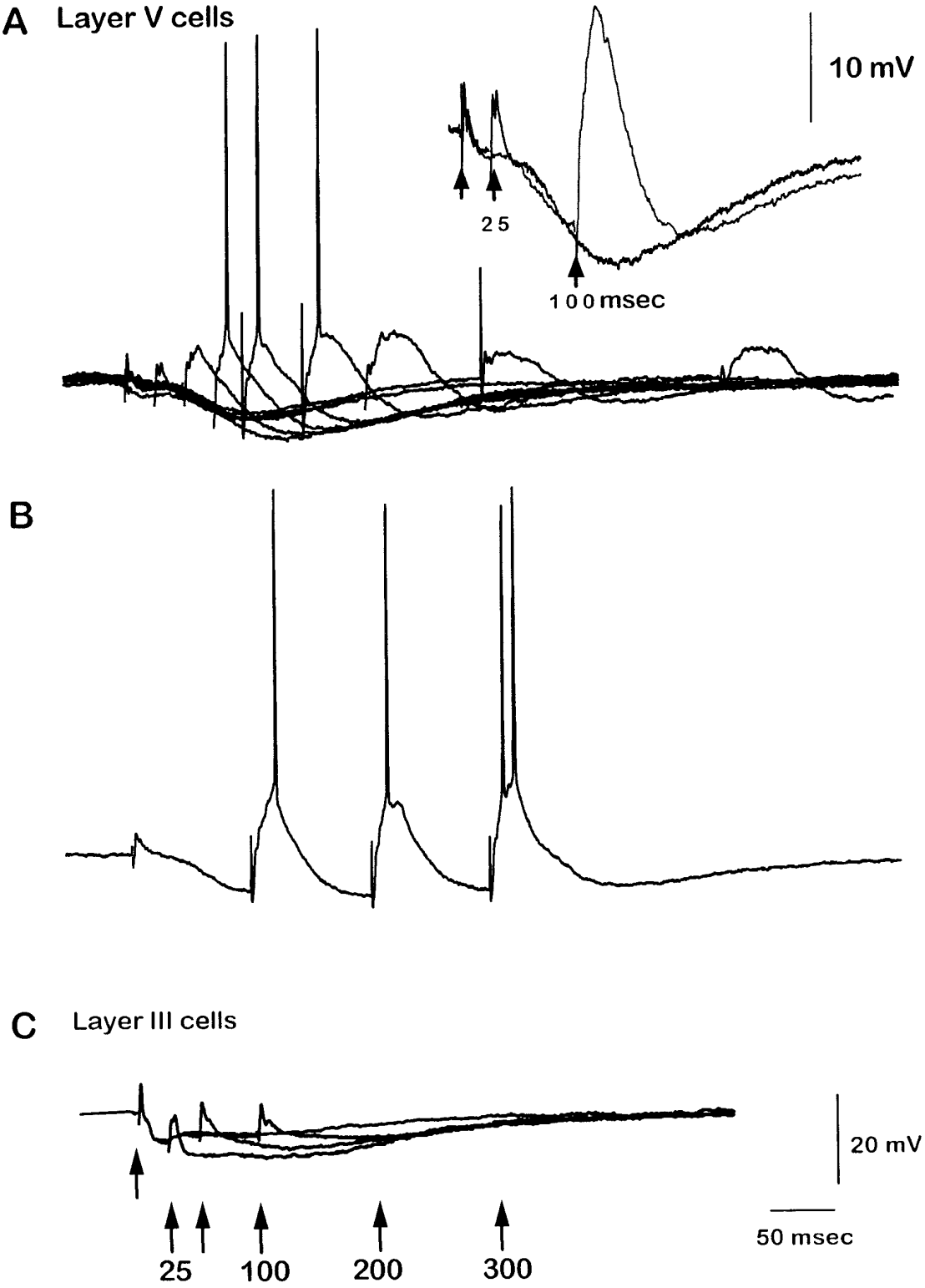

Figure 5. Augmenting responses are generated by layer V cells *in vitro*. *A*, Intracellular recording from a regular-spiking (nonadapting) layer V cell in the sensorimotor neocortex. Paired stimuli were delivered at different intervals (15, 25, 50, 75, 100, 150, 200, 300, and 500 sec), and an augmenting response was most prominent at 75, 100, and 150 msec intervals (*long traces*). Note also an enhanced response at other intervals, coincident with an apparent depression of short-latency inhibition. The *inset traces* show a different layer V cell with a particularly strong augmenting response at an interval of 100 msec. *B*, Four stimuli delivered at 10 Hz to another layer V cell show the incremental nature of the augmenting response in the slice. *C*, Intracellular recordings from a regular-spiking layer III cell in the slice. Paired stimuli delivered at different intervals generated only depression after the second stimulus at all intervals up to 5 sec (shown are 25, 50, and 100 msec). Baseline V_m is −63 mV for *A* and *B*, and −65 mV for the cell in *C*.

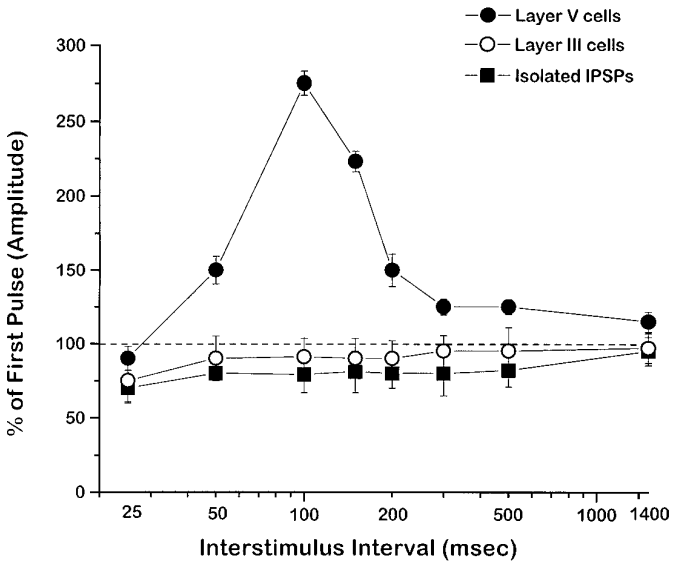

Figure 6. Frequency-dependent depression of IPSPs is not responsible for the augmenting response. Effects of paired-pulse stimulation *in vitro*. Data are expressed as a percentage of the change in the amplitude (excluding action potentials in layer V cells) of the second response, compared with the first response, in layer V cells (*closed circles*; $n = 3$), layer III cells (*open circles*; $n = 3$), and isolated IPSPs (recorded in the presence of AP5 and CNQX) from layer V cells (*closed squares*; $n = 3$). Note that IPSPs do not depress selectively at the intervals at which augmenting responses are generated more prominently in layer V cells *in vitro*.

resting potentials and input resistances, all had fast (~1 msec duration at half amplitude) action potentials of relatively low amplitude (<50 mV), and most also had longer-lasting (1–13 msec) spikes that were elicited by current injection or synaptic stimulation and always followed the fast spikes (Figs. 3, 8*A*, 9*A*) (Pockberger, 1991; Amitai et al., 1993; Kim and Connors, 1993; Stuart and Sakmann, 1994).

Intradendritic recordings *in vivo* displayed strong augmenting responses (Fig. 8*B,C*), and they did so with relatively long latencies (Figs. 2*B*, 3), as described above. Within dendrites, the first VL stimulus evoked a small, subthreshold EPSP, whereas a second stimulus 100 msec later elicited a fast spike followed by a long-lasting spike. Repetitive stimuli at 10 Hz affected the two types of spikes oppositely: fast spikes were progressively attenuated (Fig. 8*C*, *arrows*), whereas slow spikes were progressively enhanced in parallel with the augmenting response recorded extracellularly (Fig. 3; *stars* in Fig. 8*C*). The VL-evoked augmenting responses recorded in dendrites *in vivo* were subject to the same restricted range of interstimulus intervals (between 50 and 200 msec) as were augmenting responses recorded by other means (Fig. 8*B*).

Dendrites *in vitro* could generate fast and slow spikes in response to either intradendritic current injection (Fig. 9*A*) or synaptic stimulation (Fig. 9*B*). In response to paired synaptic stimuli, the duration of the long-lasting spike component increased (Fig. 9*C*); this occurred over a wide range of interstimulus intervals (25 to >500 msec) and was observed in every dendritic recording in the slice ($n = 10$).

The divergent responses of the two dendritic spike types during repetitive activation suggest that layer V pyramidal cells have independent sites for triggering fast spikes (i.e., axon initial segment; Stuart and Sakmann, 1994) and the long-lasting spike (i.e., apical dendrites; Kim and Connors, 1993; Yuste et al., 1994; also see Wong and Stewart, 1992, regarding hippocampal pyramidal cells). This is supported by somatic recordings from intrinsically bursting layer V cells ($n = 4$), which show that on depolarization by current injection to the soma, three states of response can be distinguished: a repetitive-bursting mode, a regular-spiking mode, and a fast–slow spiking mode (Fig. 10). Presumably, sufficient current injection in the soma of these cells is able to trigger the long-lasting spikes, which are generated away from the somatic region. This is consistent with recent evidence using dual impalements and imaging of layer V cells in the slice that have revealed the independent generation sites of these spikes (Yuste and Tank, 1996).

DISCUSSION

In previous studies we described some of the spatiotemporal properties of the augmenting response in the VL thalamus-to-sensorimotor cortex pathway (Castro-Alamancos and Connors, 1996b,c). The results suggested that the augmenting response is initiated by neurons within neocortical layer V. Here we have examined the cellular characteristics of the augmenting response in more detail. The main results are that (1) the augmenting response begins in neurons of layer V and appears in neurons of the upper layers during the next 5 msec; (2) the adequate interval range to produce an augmenting response (between 50 and 200 msec) parallels a strong IPSP in layer V neurons, and its termination is coincident with a long-latency depolarization; (3) layer V has a subpopulation of neurons with slow voltage-dependent conductances that serve to increase membrane excitability after hyperpolarization; (4) the priming of an augmenting response does not require presynaptic afferent activity; (5) frequency-dependent depression of synaptic inhibition far outlasts the interval range of the augmenting response; and (6) slow spiking mechanisms in active dendrites may facilitate the upward propagation of augmenting responses. These results place significant constraints on the possible cellular mechanisms of the augmenting response. We will first discuss the physiology of the augmenting response, then outline a novel hypothesis that seems consistent with the data, and finally examine it critically in the context of previous studies and proposals.

Cellular properties of neocortex critical to augmenting responses

In previous studies using current-source density analysis, we showed that the middle layer negativity of the augmenting response corresponds to a current sink in layer V, whereas the surface positivity corresponds to a current source in the upper layers (Castro-Alamancos and Connors, 1996b,c). This is consistent with the augmenting response being initiated by pyramidal cells with somata in layer V and apical dendrites projecting through supragranular layers into layer I, as our intracellular data imply.

Generation of the augmenting response in the VL-to-motor cortex pathway depends on various factors, including synaptic physiology, intrinsic membrane properties, thalamocortical connectivity, and intracortical connectivity. The laminar projection of the VL afferents to layer V may be particularly critical in this system. A thalamocortical projection to an overlapping region of cortex that avoids layer V (i.e., the ventroposterior lateral nucleus projection) does not generate augmenting responses, but rather another form of short-term plasticity, the decremental response (Castro-Alamancos and Connors, 1996b). There are several tha-

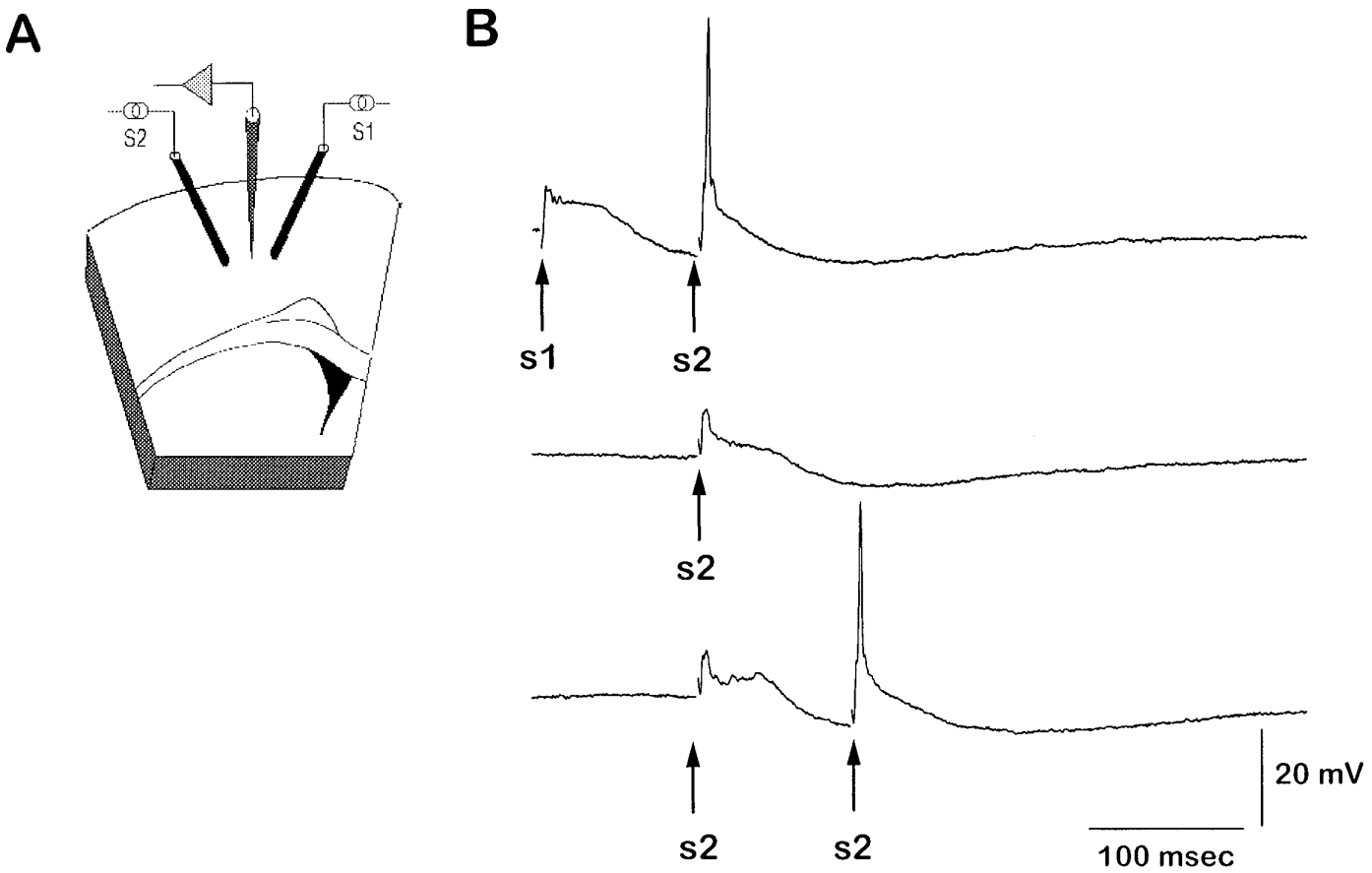

Figure 7. Presynaptic facilitation is not responsible for generating the augmenting response. *A*, Schematic diagram illustrating the location of the intracellular recording electrode in layer V and stimulating electrodes (*S1* and *S2*) activating two independent pathways to the recorded cell *in vitro*. *B*, A stimulus to S1 was capable of priming the cell so that a subsequent stimulus to S2, 100 msec later, produced an augmented response (*top trace*) similar to the augmented response observed after two stimuli are delivered to S2 (*bottom trace*). This result suggests that presynaptic mechanisms are unlikely to be of primary importance in the mechanisms of initiation of augmenting responses. Spike amplitude is filtered. Baseline V_m is −63 mV.

lamic nuclei that project to layer V and tend to avoid layer IV of the primary neocortical areas, including VL, the posterior nucleus (Po), and the lateral-posterior nucleus (LP). Herkenham (1986) called these the "paralaminar nuclei," because they also project to layer I. It would be interesting to test whether in other neocortical areas (e.g., visual cortex, barrel cortex) layer V-projecting (e.g., LP, Po) and layer IV-projecting [e.g., lateral geniculate nucleus (LGN), ventroposterior medial nucleus (VPM)] thalamic nuclei generate augmenting and decremental responses, respectively. Indeed, some evidence indicates that this may be the case (Steriade, 1991).

Our results indicate that hyperpolarization-dependent conductances may be crucial for generating the augmenting response. In the rat neocortex, these currents seem to be selectively concentrated in a subpopulation of layer V cells. We observed that hyperpolarizing current injection produced a voltage sag shortly after current onset and a rebound depolarization after current offset. These characteristics often indicate hyperpolarization-activated cation currents (I_H) and low-threshold calcium currents (I_T), respectively (Deschenes et al., 1984; Jahnsen and Llinas, 1984; Wang and McCormick, 1993). Evidence for I_T has been described repeatedly in neocortical cells (Friedman and Gutnick, 1987; Sutor and Zieglgansberger, 1987; Hamill et al., 1991; Silva et al., 1991; Wang and McCormick, 1993); it is differentially distributed among pyramidal cell types (Giffin et al., 1991) and may present different forms in different cell types (Huguenard and Prince, 1992). I_T probably also exists in a subpopulation of neocortical GABA-containing interneurons (Kawaguchi, 1993, 1995). I_H has also been observed in neocortical layer V cells (Spain et al., 1987, 1991), especially in the repetitively bursting pyramidal cells (Wang and McCormick, 1993), but not in layer II–III cells (van Brederode and Spain, 1995). Indeed, these layer V cells recorded *in vivo* display augmenting responses to afferent stimuli (Steriade et al., 1993) and rhythmic bursts within the frequency range of the augmenting response (Nuñez et al., 1993).

The effective interstimulus interval for the augmenting response is between 50 and 200 msec. Some physiological phenomenon occurring during this period, triggered by the first pulse, must prime the cortex for the induction of the augmenting response. Thalamic afferent stimulation generates strong membrane hyperpolarization of pyramidal cells, initially attributable to activation of $GABA_A$ receptors and at longer latencies attributable to $GABA_B$ receptor activation (Connors et al., 1988; van Brederode and Spain, 1995), and it does so via rapid excitation of inhibitory interneurons (Douglas and Martin, 1991; Agmon and Connors, 1992). Inhibitory hyperpolarization seems to be an essential priming step for the augmenting response.

Activation of VL afferents *in vivo* always led to a long-latency (175–200 msec) depolarization, either after a single stimulus or after the last pulse of a stimulus train. This long-latency depolar-

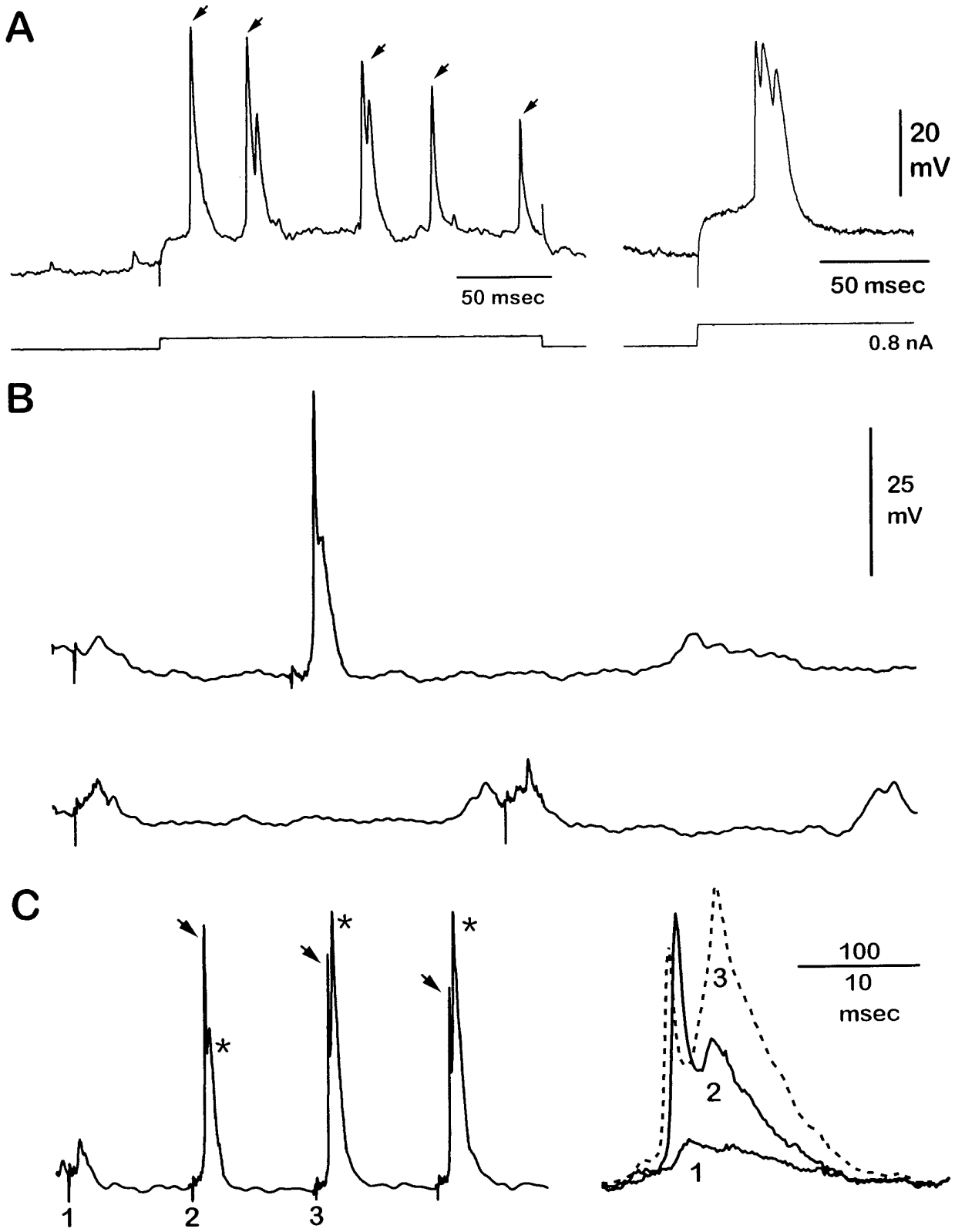

Figure 8. Intracellular recording from dendrites located in layer III *in vivo*. *A*, Intracellularly injected current pulses produced progressively attenuating fast spikes and longer-lasting spikes. *B*, Paired pulses at a 100 msec interval (*top*), but not at 200 msec (*bottom*), produced an augmenting response consisting of a fast spike, a longer-lasting spike, and synaptic components. *C*, In response to a short train of VL stimulation at 10 Hz, the augmenting response recorded from another dendrite in layer III shows progressive attenuation of the fast spikes (*arrows*) and a strong enhancement of a longer-lasting spike (*asterisks*). The overlapping traces at *right* show the first (*1*), second (*2*), and third (*3*) responses of the dendrite at faster sweep speed. Note the enhancement of the long-lasting spike and attenuation of the fast spike.

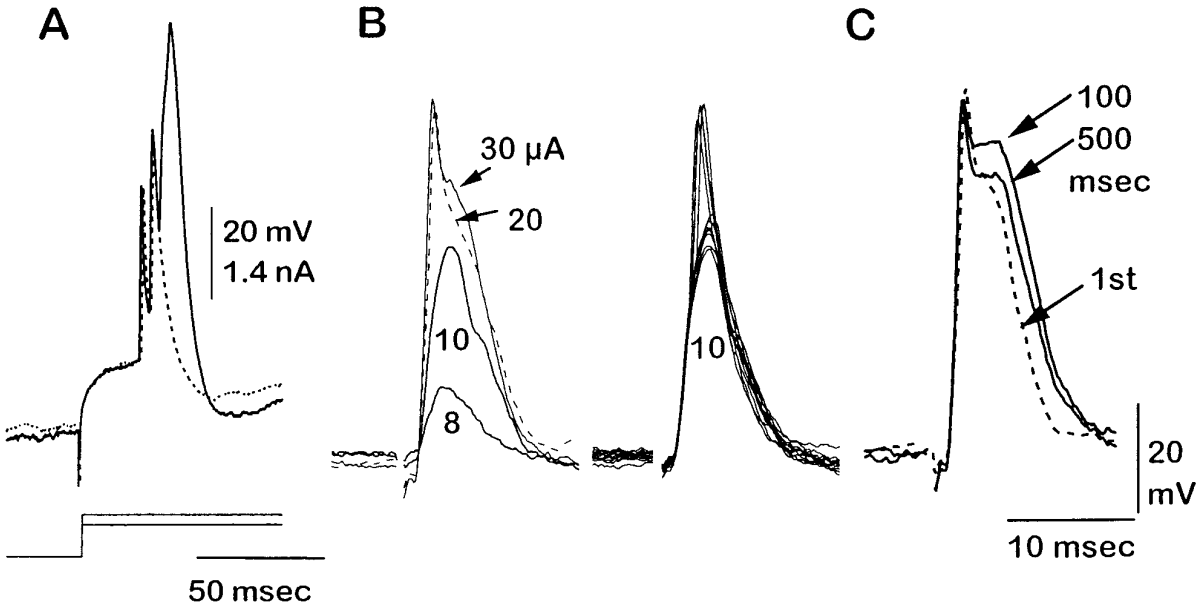

Figure 9. Intracellular recordings from dendrites in layer III *in vitro*. *A*, Current pulses produced fast spikes and long-lasting spikes in intradendritic recordings from layer III. *B*, Synaptic stimulation in layer V applied at different intensities produce graded synaptic responses and all-or-none spike components (*left traces*). At 10 μA current intensity a threshold was observed for the induction of the fast spike. Shown are 12 trials at 0.1 Hz (*right traces*). Note that the fast spike appears on approximately half of those trials at this threshold stimulation. *C*, Paired stimuli at a range of interstimulus intervals (shown are 100 and 500 msec) produce an enhancement of the long-lasting spike and attenuation of the fast spike. The *dashed line* is the control response to the first stimulus, and the *overlapping traces* correspond to the second response delivered at different interstimulus intervals.

ization interrupted the inhibitory hyperpolarization of layer V cells and marked the longest effective interval for augmenting responses. We suggest that the long-latency potential is a combination of intrinsic membrane events generated by low-threshold currents and synaptic excitation generated by local axonal collaterals of pyramidal cells. Rebound potentials of a similar sort have been described in the thalamus where they are known to be attributable to activation of voltage-dependent conductances in relay and reticular nucleus neurons (Steriade, 1984; Steriade and Llinas, 1988; Steriade et al., 1990). The long-latency depolarization may mark the end of the effective interval for the augmenting response, because it leads to the inactivation of the essential intrinsic currents; these currents become available again only when cells are primed by another inhibitory hyperpolarization.

The role of dendritic electrogenesis

Active membrane currents have been demonstrated in the dendrites of many neurons. For instance, Purkinje cell dendrites are dominated by active Ca^{2+} currents (Llinas and Sugimori, 1980), whereas hippocampal dendrites have Na^{+}- as well as Ca^{2+}-dependent conductances (Spruston et al., 1995). Pyramidal cells in layer V of neocortex are diverse in structure and electrophysiology (Connors et al., 1996), and they also vary in dendritic electrogenesis (Kim and Connors, 1993). Thus, the apical dendrites of large layer V pyramidal cells express both voltage-dependent Na^{+} currents (Huguenard et al., 1989; Kim and Connors, 1993; Stuart and Sakmann, 1994) and Ca^{2+} currents (Amitai et al., 1993; Kim and Connors, 1993). In fact, these dendritic conductances allow the active back-propagation of the sodium-dependent action potentials, initiated in the axon, into the apical dendrites (Stuart and Sakmann, 1994). Interestingly, back-propagation of fast spikes shows an activity-dependent attenuation attributable to, for example, failure of transmission at branch points and/or current inactivation (Spruston et al., 1995).

In this study we showed that potentials recorded from apical dendrites located in the upper layers do not contribute to the initiation of the augmenting response, because their latency is quite long. More likely, retrograde intradendritic potentials contribute to the spread of augmented activity to the upper layers in at least two ways: back-propagating action potentials (fast spikes) and Ca^{2+}-dependent dendritic spikes (long-lasting spikes). In our dendritic recordings, fast spikes were strongly attenuated during repeated synaptic stimulation or steady current injection, similar to the behavior of CA1 dendrites (Spruston et al., 1995). Fast-spike attenuation may result from membrane depolarization and channel inactivation, leading to progressively more passive back-propagation during incremental augmenting responses. More interestingly, the long-lasting spikes recorded from the same dendritic sites were apparently facilitated during the augmenting response. Thus, the long-lasting spike, which is Ca^{2+}-dependent (Kim and Connors, 1993), contributes to the upward, intradendritic spread of augmenting activity. The implications of this back-propagating activity remain to be elucidated, but it is possible that the effects of retrograde dendritic spikes on postsynaptic membrane potential could influence the plasticity of concurrently active dendritic synapses.

A hypothesis for the generation of the augmenting response

We propose that the augmenting response arises from the following cellular mechanisms. Axons from VL thalamus terminate within layer V (Herkenham, 1980; Castro-Alamancos and Connors, 1996b,c) and directly excite both pyramidal cells and inhibitory interneurons in layer V. The ensuing strong hyperpolarization of layer V pyramidal cells, generated by feedforward inhibition, activates currents such as the hyperpolarization-activated cation current (I_H) and deinactivates currents such as the low threshold calcium current (I_T). If there is subsequent activity in VL afferents during this hyper-

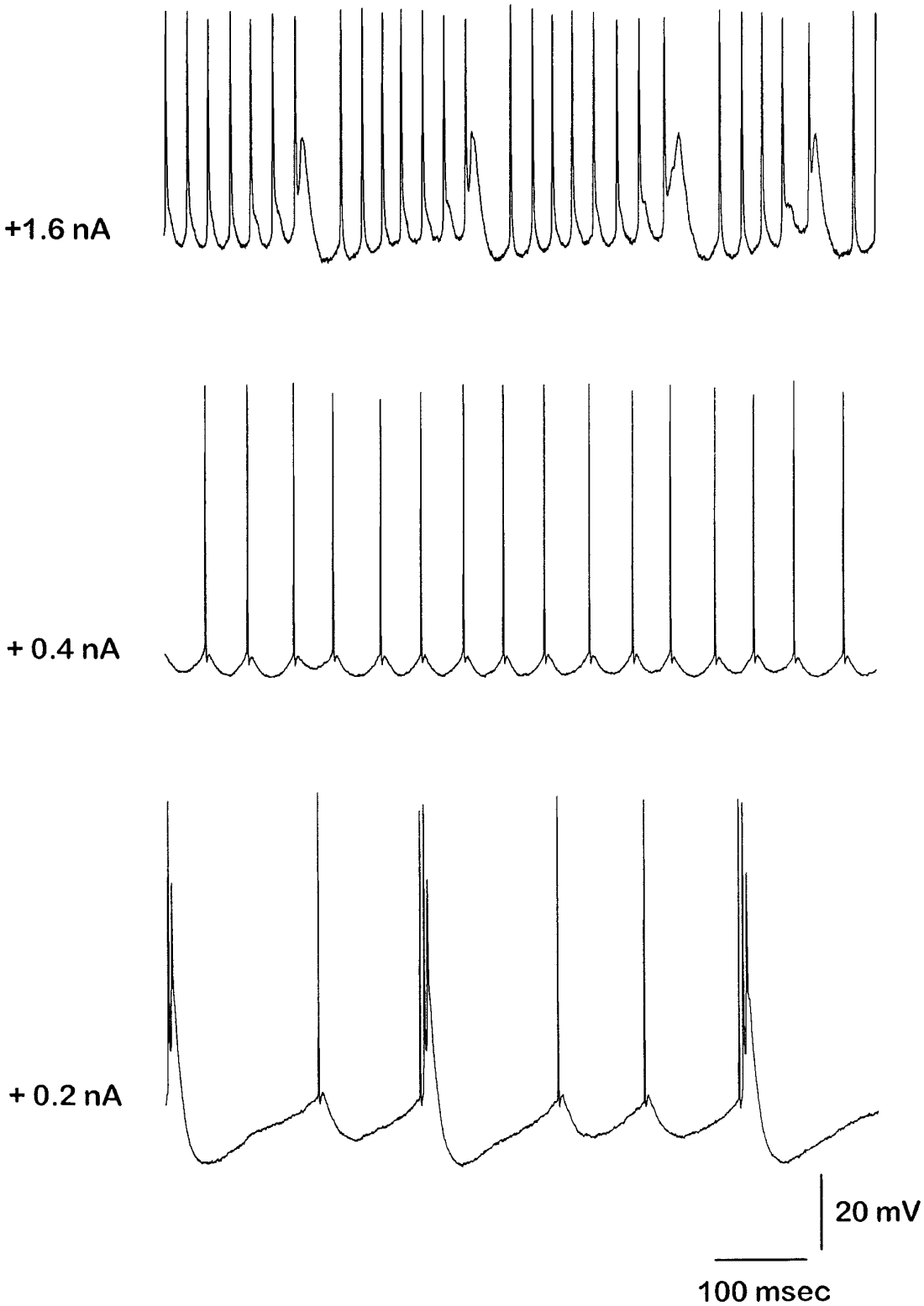

Figure 10. High-threshold, long-lasting spikes can be observed in somatic recordings of repetitively bursting cells in layer V. Intracellular recording from a layer V repetitively bursting cell during three levels of depolarizing constant current injection. Low current (0.2 nA) generated a mix of fast spikes and bursts, moderate current (0.4 nA) triggered rhythmic fast spikes, and strong current (1.6 nA) evoked attenuated fast spikes interspersed with fast-spike/slow-spike complexes.

polarization, it yields a larger (augmented) response because of (1) inward I_H and the activation of now deinactivated I_T-like currents in layer V pyramidal cells, (2) network-dependent reinforcement by extensive excitatory interconnections between layer V pyramidal cells (Connors and Amitai, 1995; Douglas et al., 1995), (3) spread of activity to upper layers via interlaminar excitatory connections and backpropagating action potentials in the apical dendrites of layer V cells, and (4) spread to adjacent regions of cortex via horizontal collaterals.

There are several defining characteristics of the augmenting response that are explained by our hypothesis. Its surface positivity and middle layer negativity in extracellular recordings arise because it originates with inward currents (intrinsic and synaptic) in vertically extended layer V pyramidal cells. The onset of the effective interstimulus interval, at a latency of ~50 msec, is determined by the need for sufficient IPSP-driven hyperpolarization to influence intrinsic, voltage-dependent membrane currents. The termination of the effective interval is coincident with the long-latency depolarization that follows VL stimulation by ~200 msec. This depolarization is attributable to rebound excitation within the network of layer V neurons, which is manifest as a spatially and temporally distributed EPSP; it determines the end of the augmenting interval because its depolarization inactivates the essential intrinsic currents that would otherwise boost VL-generated synaptic currents.

Comparison to previous hypotheses for the augmenting response

Various hypotheses have been proposed for the cellular mechanisms of the augmenting response. An early proposal, based on intracellular recordings and VL stimulation in the cat, was that the augmenting response arose from a marked increase in the magnitude of long-latency EPSPs, attributable to the stimulus-dependent depression of inhibition (Purpura and Shofer, 1964; Creutzfeldt et al., 1966). A similar and more recent hypothesis is that long-latency facilitated EPSPs are NMDA receptor-mediated potentials (Metherate and Ashe, 1994). Several observations indicate that depression of inhibition may contribute to the augmenting response, but that it is not the primary mechanism. First, the amount of facilitation attributable to depressed inhibition reported for paired-pulse stimulation is considerably smaller than the facilitation displayed by the augmenting response. Thus, although augmenting responses increase severalfold over control responses, the facilitation attributable to a release from inhibition by paired pulses is normally <50% (Metherate and Ashe, 1994). Second, the interstimulus interval range effective in depressing inhibition is much wider than the effective range for generating the augmenting response. Metherate and Ashe (1994) reported that facilitation of EPSPs attributable to release from inhibition was effective for interstimulus intervals from 100 to 1000 msec and was apparent even after 10 sec. This is consistent with our own measurements of isolated IPSPs (Fig. 6). The augmenting response, however, occurs during a very narrow time period of between 50 and 200 msec. Third, release from inhibition facilitates mainly a long-latency potential in the neocortex that is mediated by NMDA receptor-dependent conductances. This implies that NMDA receptors are essential for the augmenting response and NMDA receptor antagonists should abolish or strongly depress it; however, this is not the case (Addae and Stone, 1987; Castro-Alamancos and Connors, 1996b). Finally, the IPSP depression hypothesis does not explain the nature of the long-latency depolarization and its coincidence with the end of the effective augmenting interval or the selective involvement of layer V in the augmenting process. Cells in upper layers also undergo frequency-dependent enhancement of EPSPs caused by the depression of IPSPs (Castro-Alamancos and Connors, 1996a), but they do not initiate augmenting responses (Castro-Alamancos and Connors, 1996b).

Ferster and Lindstrom (1985a) provided an alternative view of the augmenting response, based on their investigations of connections between the LGN and primary visual cortex in cats. They observed an incremental cortical response during strong (i.e., 1 mA) repetitive LGN stimulation and proposed that it was dependent on antidromic firing of layer VI corticothalamic axons and the singular properties of the synapses on their intracortical collaterals. This hypothesis requires that the intracortical synapses of corticothalamic cells show strong paired-pulse facilitation, a form of short-term plasticity mediated presynaptically (Zucker, 1989). Paired-pulse facilitation is usually not observed in excitatory synapses of neocortex (Thomson et al., 1993; Volgushev et al., 1995), although it is certainly possible that these specific synapses show it (Thomson et al., 1995). Nevertheless, this hypothesis is not consistent with several properties of the augmenting response. First, paired-pulse facilitation is most prominent between 25 and 75 msec (maximal at 50 msec) under normal conditions in the Schaffer-collateral pathway in hippocampal CA1 and also in neocortex under low probability of release conditions (i.e., lower than normal calcium concentration; M. Castro-Alamancos and B. Connors, unpublished observations), whereas the augmenting response is just beginning at 50 msec and peaks in size at 150–175 msec, just before the occurrence of the long-latency potential. Second, previous studies have found no evidence for antidromic firing of corticothalamic cells during augmenting responses elicited with moderate stimulation currents (Castro-Alamancos and Connors, 1996b). Ferster and Lindstrom (1985a,b) used stimulation currents 10-fold higher than we typically use to evoke augmenting responses. Corticothalamic axons tend to be much slower, with higher threshold, than thalamocortical axons (Ferster and Lindstrom, 1983; Swadlow, 1994). Third, we found that a presynaptic mechanism is unlikely to account for the generation of the augmenting response, because two independent but convergent pathways can prime the augmenting responses to one other. Pure synaptic facilitation is usually attributed to presynaptic processes (Zucker, 1989). Finally, this hypothesis cannot account for the relevance of the inhibitory hyperpolarization or of the long-latency depolarization and the timing of the augmenting response.

In contrast to the previous two hypotheses, the general proposal of Morin and Steriade (1981) is consistent with the results presented here. They concluded that the augmenting response depends critically on the hyperpolarization of cortical cells.

Implications for behavioral modulation of the augmenting response

We recently observed that the generation of the augmenting response depends strongly on the awake behavioral state of the animal (Castro-Alamancos and Connors, 1996c); augmenting responses are robust during periods of awake immobility but are abolished rapidly during states of arousal and movement. Interestingly, stimulation of the reticular midbrain inactivates augmenting responses (Steriade and Morin, 1981) in a manner reminiscent of the behavioral inactivation. The behavioral modulation

of the augmenting response may arise from the actions of certain neurotransmitters (i.e., acetylcholine, norepinephrine) that are released in neocortex during behaviorally activated states (Aston-Jones et al., 1991; Cooper et al., 1991). These transmitters can transform or block the firing properties and intrinsic membrane currents of the layer V cells essential for generating the augmenting response (Wang and McCormick, 1993). They can also modulate synaptic inhibition presynaptically (Doze et al., 1991). Thus, our hypothesis for the mechanisms of the augmenting response suggests critical sites at which modulatory transmitters might selectively control thalamocortical dynamics during changes of behavioral state.

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