Impact of Network Activity on the Integrative Properties of Neocortical Pyramidal Neurons In Vivo

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Destexhe, Alain and Denis Paré. Impact of network activity on the integrative properties of neocortical pyramidal neurons in vivo. J. Neurophysiol. 81: 1531–1547, 1999. During wakefulness, neocortical neurons are subjected to an intense synaptic bombardment. To assess the consequences of this background activity for the integrative properties of pyramidal neurons, we constrained biophysical models with in vivo intracellulart data obtained in anesthetized cats during periods of intense network activity similar to that observed in the waking state. In pyramidal cells of the parietal cortex (area 5–7), synaptic activity was responsible for an approximately fivefold decrease in input resistance (Rin), a more depolarized membrane potential (Vm), and a marked increase in the amplitude of Vm fluctuations, as determined by comparing the same cells before and after microperfusion of tetrodotoxin (TTX). The model was constrained by measurements of Rin, by the average value and standard deviation of the Vm measured from epochs of intense synaptic activity recorded with KAc or KCl-filled pipettes as well as the values measured in the same cells after TTX. To reproduce all experimental results, the simulated synaptic activity had to be of relatively high frequency (1–5 Hz) at excitatory and inhibitory synapses. In addition, synaptic inputs had to be significantly correlated (correlation coefficient ~0.1) to reproduce the amplitude of Vm fluctuations recorded experimentally. The presence of voltage-dependent K+ currents, estimated from current-voltage relations after TTX, affected these parameters by <10%. The model predicts that the conductance due to synaptic activity is 7–30 times larger than the somatic leak conductance to be consistent with the approximately fivefold change in Rin. The impact of this massive increase in conductance on dendritic attenuation was investigated for passive neurons and neurons with voltage-dependent Na+/K+ currents in soma and dendrites. In passive neurons, correlated synaptic bombardment had a major influence on dendritic attenuation. The electrotonic attenuation of simulated synaptic inputs was enhanced greatly in the presence of synaptic bombardment, with distal synapses having minimal effects at the soma. Similarly, in the presence of dendritic voltage-dependent currents, the convergence of hundreds of synaptic inputs was required to evoke action potentials reliably. In this case, however, dendritic voltage-dependent currents minimized the variability due to input location, with distal apical synapses being as effective as synapses on basal dendrites. In conclusion, this combination of intracellular and computational data suggests that, during low-amplitude fast electroencephalographic activity, neocortical neurons are bombarded continuously by correlated synaptic inputs at high frequency, which significantly affect their integrative properties. A series of predictions are suggested to test this model.

INTRODUCTION

Since the classical view of passive dendritic integration was proposed for motoneurons 30 years ago (Fatt 1957), the introduction of new experimental techniques such as intradendritic recordings (Llinás and Nicholson 1971; Wong et al. 1979), and visually guided patch-clamp recording (Stuart et al. 1993; Yuste and Tank 1996) has revolutionized this area. These new approaches revealed that the dendrites of pyramidal neurons are involved actively in the integration of excitatory postsynaptic potentials (EPSPs) and that the activation of few synapses has powerful effects at the soma in brain slices (Markram et al. 1997; Mason et al. 1991; Thomson and Deuchars 1997). Although remarkably precise data have been obtained in slices, little is known about the integrative properties of the same neurons in vivo.

The synaptic connectivity of the neocortex is very dense. Each pyramidal cell receives 5,000–60,000 synapses (Cragg 1967; DeFelipe and Faríñas 1992), 70% of which originate from other cortical neurons (Gruner et al. 1974; Szentagothai 1965). Given that neocortical neurons spontaneously fire at 5–20 Hz in awake animals (Evarts 1964; Hubel 1959; Steriade 1978), cortical cells must experience tremendous synaptic currents that may have a significant influence on their integrative properties. This theme was explored by several modeling studies (Barrett 1975; Bernard et al. 1991; Holmes and Woody 1989), where it was predicted that synaptic activity may have a profound impact on dendritic integration. However, despite its possible importance for understanding neuronal function, the conductance due to synaptic activity was never measured in awake animals because of the paramount technical difficulties related to intracellular recordings in conscious animals.

To circumvent these difficulties, we constrained computational models of neocortical pyramidal neurons with in vivo intracellular data obtained in ketamine-xylazine-anesthetized cats before and after local perfusion of tetrodotoxin (TTX) (Paré et al. 1998b). The interest of this approach derives from the fact that under ketamine-xylazine anesthesia, cortical neurons oscillate (~1 Hz) between two states, one where the network is quiescent and another where it displays a pattern of activity similar to the waking state (Steriade et al. 1993a,b) (Fig. 1A and B). Indeed, during these active periods (Fig. 1B, underlined epochs), as in the waking state (Fig. 1A), the electroencephalogram (EEG) is dominated by waves of low amplitude and high frequencies (20–60 Hz) and neocortical pyramidal neurons fire spontaneously at 5–20 Hz. Moreover, electrical stimulation of brain stem activating systems that are believed to maintain the awake state in normal circumstances elicits periods of desynchronized EEG activity with similar characteristics under ketamine-xylazine anesthesia (Steriade et al. 1993a).

Thus we estimated the synaptic activity required to account...
for the differences in neuronal properties observed in vivo during synaptic quiescence (i.e., in the presence of TTX) and during these active periods, here considered as a model of the spontaneous synaptic bombardment occurring in the waking state. The model then was used to infer the impact of this intense synaptic activity on dendritic integration.

**METHODS**

**Intracellular recordings in vivo**

We reanalyzed intracellular data obtained from neocortical pyramidal cells recorded in a previous study (Paré et al. 1998b). Unpublished intracellular recordings obtained with K-acetate-filled pipettes \((n = 2)\) also were included in the analysis. Briefly, intracellular recordings were obtained from morphologically identified neocortical pyramidal cells in the suprasylvian gyrus (area 5–7) of cats deeply anesthetized with a ketamine-xylazine mixture (11 and 2 mg/kg im), paralyzed with gallamine triethiodide, and artificially ventilated. The level of anesthesia was determined by continuously monitoring the EEG, and supplemental doses of ketamine-xylazine (2 and 0.3 mg/kg, respectively, iv) were given to maintain a synchronized EEG pattern. Lidocaine (2%) was applied to all skin incisions. End-tidal \(\text{CO}_2\) concentration was kept at 3.7 \(\pm\) 0.2% (mean \(\pm\) SE) and the body temperature was maintained at 37°C with a heating pad. To ensure recording stability, the cisterna magna was drained, the cat was suspended, and a bilateral pneumothorax was performed. Intracellular recording electrodes consisted of glass capillary tubes pulled to a tip diameter of \(\approx 0.5\) \(\mu\)m(\(\approx 30\) M\(V\)), and filled with K-acetate or KCl (2.5 M). Details about experimental procedures and cell identification were given previously (Paré et al. 1998a,b). Experiments were conducted in agreement with ethics guidelines of the Canadian Council on Animal Care.

**TTX microperfusion in vivo**

An injection micro-pipette (75 \(\mu\)m tip diameter) was inserted \(\approx 2\) mm rostral to the recording micropipette to a depth of 1.5 mm. A solution (Ringer or Ringer + TTX, 50 \(\mu\)M) was pumped continuously through the injection pipette (1–1.5 \(\mu\)l/min) for the duration of the recording session; the dialyzing solution was changed using a liquid switch system. The Ringer solution contained (in mM) 126 NaCl, 26 NaHCO\(_3\), 3 KCl, 1.2 KH\(_2\)PO\(_4\), 1.6 MgSO\(_4\), 2 CaCl\(_2\), 5 HEPES, and 15 glucose. The blockade of synaptic activity by TTX was evidenced by the disappearance of responses to electrical stimuli applied to the
cortex using tungsten microelectrodes inserted 2 mm caudal to the recording pipette (see Paré et al. 1997, 1998b for more details).

**Estimation of membrane parameters**

Membrane potential ($V_m$) distributions were computed from concatenated epochs of intense synaptic activity totaling ~1 min. The signal was sampled at 5 kHz (for a total of ~300,000 data points), and the positive phase of action potentials was deleted digitally. The values of these data points (usually 2) were replaced by that of points immediately preceding the action potentials. No attempt was made to delete spike afterpotentials because they were distorted by spontaneous synaptic events. The average $V_m$ ($\langle V_m \rangle$) and the standard deviation ($\sigma_v$) were computed from such distributions.

**Geometry for computational models**

Simulations of cat layer II–III, layer V, and layer VI neocortical pyramidal cells were based on cellular reconstructions obtained from two previous studies (Contreras et al. 1997; Douglas et al. 1991). The cellular geometries were incorporated into the NEURON simulation environment (Hines and Carnevale 1997). The dendritic surface was corrected for spines, assuming that spines represent ~45% of the dendritic membrane area (DeFelipe and Fariñas 1992). Surface correction was made by rescaling $C_m$ and conductances by 1.45 as described previously (Bush and Sejnowski 1993; Paré et al. 1998a). An axon was added, consisting in an initial segment of 20 $\mu$m length and 1 $\mu$m diameter, followed by 10 segments of 100 $\mu$m length and 0.5 $\mu$m diameter each.

**Passive properties**

Passive properties were adjusted to experimental recordings in the absence of synaptic activity: to block synaptic events mediated by glutamate $\alpha$-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and $\gamma$-aminobutyric acid type-A (GABA_A) receptors, the microperfusion solution contained: Ringer and reversal potential, whereas other passive parameters were fixed. The kinetics of AMPA and GABA_A receptor types were simulated using two-state kinetic models (Destexhe et al. 1994)

$$I_{syn} = g_{syn} m (V - E_{syn})$$

$$\frac{dm}{dt} = \alpha [T] (1 - m) - \beta m$$

where $I_{syn}$ is the postsynaptic current, $g_{syn}$ is the maximal conductance, $m$ is the fraction of open receptors, $E_{syn}$ is the reversal potential, $[T]$ is the transmitter concentration in the left, and $\alpha$ and $\beta$ are forward and backward binding rate constants of $T$ to open the receptors. $E_{syn} = 0$ mV, $\alpha = 1.1 \times 10^8 M^{-1}s^{-1}$, $\beta = 670 s^{-1}$ for AMPA receptors; $E_{syn} = -80$ mV, $\alpha = 5 \times 10^6 M^{-1}s^{-1}$, $\beta = 180 s^{-1}$ for GABA_A receptors. When a spike occurred in the presynaptic compartment, a pulse of transmitter was triggered such that $[T] = 1$ mM during 1 ms. The kinetic parameters were obtained by fitting the model to postsynaptic currents recorded experimentally (see Destexhe et al. 1998). $N$-methyl-$d$-aspartate (NMDA) receptors are blocked by ketamine and were not included.

**Correlation of release events**

In some simulations, $N$ Poisson-distributed random presynaptic trains of action potentials were generated according to a correlation coefficient $c$. The correlation applied to any pair of presynaptic train, irrespective of the proximity of synapses on the dendritic tree and correlations were treated independently for excitatory and inhibitory synapses for simplicity. To generate correlated presynaptic trains, a set of $N_2$ independent Poisson-distributed random variables was generated and distributed randomly among the $N$ presynaptic trains. This procedure was repeated at every integration step such that the $N_2$ random variables were redistributed constantly among the $N$ presynaptic trains. Correlations arose from the fact that $N_2 \leq N$ and the ensuing redundancy within the $N$ presynaptic trains. $N_2$ was chosen such as to generate a correlation of $c = 0.05$–0.2 calculated from the peak of the cross-correlation function. Typically, $n = 16563$ and $N_2 = 400$ gave a correlation value of $c \approx 0.1$.

**Active currents**

Active currents were inserted into the soma, dendrites, and axon with different densities in accordance with available experimental evidence in neocortical and hippocampal pyramidal neurons (Hoffman et al. 1997; Magee and Johnston 1995; Magee et al. 1998; Stuart and Sakmann 1994). Active currents were expressed by the generic form

$$I_a = g_a m^\# h^\# (V - E_a)$$

where $g_\#$ is the maximal conductance of current $I_a$ and $E_a$ is its reversal potential. The current activates according to $M$ activation gates, represented by the gating variable $m$. It inactivates with $N$ inactivation gates represented by the gating variable $h$, $m$ and $h$ obey to first-order kinetic equations.

**Voltage-dependent $Na^+$ current** was described by (Traub and Miles 1991)

$$I_{Na} = g_{Na} m^3 h (V - E_{Na})$$

$$\frac{dm}{dt} = \alpha_m(V) (1 - m) - \beta_m(V) m$$

$$\frac{dh}{dt} = \alpha_h(V) (1 - h) - \beta_h(V) h$$

where $g_{Na}$ is the maximal conductance of $Na^+$ channels, $E_{Na}$ is the reversal potential, and $\alpha$ and $\beta$ are rate constants of $Na^+$ channels.
\[
\alpha_n = \frac{-0.32(V - V_0 - 13)}{\exp[-(V - V_0 - 13)/4]} - 1
\]
\[
\beta_n = \frac{0.28(V - V_1 - 40)}{\exp((V - V_1 - 40)/5)} - 1
\]
\[
\alpha_h = 0.128 \exp[-(V - V_1 - V_5 - 17)/18] + 4
\]
\[
\beta_h = \frac{1 + \exp[-(V - V_1 - V_5 - 40)/5] - 1}{4}
\]

where \(V_1 = -58\) mV was adjusted to obtain a threshold of around \(-55\) mV as in our experiments, and the inactivation was shifted by 10 mV toward hyperpolarized values \(V_5 = -10\) mV to match the voltage dependence of \(Na^+\) currents in neocortical pyramidal cells (Huguenard et al. 1988). The pattern and kinetics of \(Na^+\) channels was similar to a previous study on hippocampal pyramidal cells (Hoffman et al. 1997): the density was low in soma and dendrites (120 pS/\(\mu\)m²) and was 10 times higher in the axon.

The “delayed-rectifier” \(K^+\) current was described by (Traub and Miles 1991)

\[
I_{k1} = g_{k1} n^4 (V - E_k)
\]
\[
\frac{dn}{dt} = \alpha_n(V) (1 - n) - \beta_n(V) n
\]
\[
\alpha_n = -0.032(V - V_1 - 15) \exp[-(V - V_1 - 15)/5] - 1
\]
\[
\beta_n = 0.5 \exp[-(V - V_1 - 10)/40]
\]

\(K^+\) channel densities were of 100 pS/\(\mu\)m² in soma and dendrites, and 1,000 pS/\(\mu\)m² in the axon.

A noninactivating \(K^+\) current was described by (Mainen et al. 1995)

\[
I_m = g_m n (V - E_k)
\]
\[
\frac{dn}{dt} = \alpha_m(V) (1 - n) - \beta_m(V) n
\]
\[
\alpha_m = 0.0001(V + 30) \exp[-(V + 30)/9]
\]
\[
\beta_m = -0.0001(V + 30) \exp[-(V + 30)/9]
\]

This current was present in soma and dendrites (density of 2–5 pS/\(\mu\)m²) and was responsible for spike frequency adaptation, as detailed previously (Paré et al. 1998a).

It was reported that some pyramidal cell have a hyperpolarization-activated current termed \(I_h\) (Spain et al. 1987; Stuart and Spruston 1998). However, most cells recorded in the present study had no apparent \(I_h\) (see passive responses in Figs. 1 and 2). Occasionally, cells displayed a pronounced \(I_h\), but these cells were not included in the present study. This current was therefore not included in the model.

All simulations were done using NEURON (Hines and Carnevale 1997) on a Sparc-20 work-station (Sun Microsystems, Mountain View, CA).

RESULTS

Membrane properties of neocortical pyramidal neurons during active periods

In a previous study (Paré et al. 1998b), the properties of pyramidal neurons were compared before and after local TTX application, revealing that differences in background synaptic activity account for much of the discrepancies between in vivo and in vitro recordings. Intracellular recordings were performed under barbiturate and ketamine-xylazine anesthesia, and the input resistance \(R_{in}\) was estimated before and after TTX application (Paré et al. 1998b). However, these properties were never measured specifically during active periods. Here, we have reexamined and quantified these data by focusing specifically on active periods occurring under ketamine-xylazine anesthesia (Fig. 1B, bars). These active periods were identified as follows: neurons fire at \(-5\)–20 Hz, their membrane potential \(V_m\) is around \(-65\) to \(-60\) mV, and the EEG displays low-amplitude waves of fast frequency in the gamma range. Active periods usually lasted \(-0.4\)–2 s, although periods lasting up to several seconds occasionally occurred (Steirae et al. 1993a).

During active periods, neocortical neurons had a low \(R_{in}\), as shown by the relatively small voltage responses to intracellular current injection (Fig. 1C, top). Averaging 50 pulses during active periods led to \(R_{in}\) of 9.2 ± 4.3 M\(\Omega\) (\(n = 26\)), consistent with previous observations (Contreras et al. 1996).

The total conductance change due to synaptic activity was quantified by comparing the \(R_{in}\) of the cells during active periods to that measured after blocking synaptic transmission using microperfusion of TTX. Under TTX, injection of current pulses led to larger responses (Fig. 1D) and larger \(R_{in}\) values (46 ± 8 M\(\Omega\); \(n = 9\)). This was paralleled by a marked decrease in the amplitude of \(V_m\) fluctuations, as quantified by the standard deviation of the \(V_m\) (\(\sigma_V\); Fig. 1E). In nine different cells recorded successively during active periods and after TTX application, \(\sigma_V\) was reduced from 4.0 ± 2.0 mV to 0.4 ± 0.1 mV, respectively (Fig. 1F). Figure 1E also shows that the \(V_m\) dropped significantly to \(-80\) ± 2 mV, as reported previously (Paré et al. 1998b). During active periods, the average \(V_m\) (\(\langle V_m \rangle\)) was \(-65\) ± 2 mV in control conditions (K-acetate-filled pipettes) and \(-51\) ± 2 mV with chloride-filled recording pipettes. These conditions correspond to chloride reversal potentials \(E_{Cl}\) of \(-73.8\) ± 1.6 mV and \(-52.0\) ± 2.9 mV, respectively (Paré et al. 1998a).

Normalizing \(R_{in}\) changes with reference to the \(R_{in}\) measured in the presence of TTX revealed that in all cells where active periods could be compared with an epoch of suppressed synaptic activity (\(n = 9\)), the \(R_{in}\) was reduced by approximately the same relative amount (81.4 ± 36%; Fig. 1F; data summarized in Table 1), independently of absolute values. Similar values were obtained by repeating this analysis at different \(V_m\), either more depolarized, by using chloride-filled pipettes (\(n = 7\), or more hyperpolarized, by steady current injection (\(-1\) nA; \(n = 2\)). Taken together, these data show that active periods are characterized by an about fivefold decrease in \(R_{in}\), a significant depolarization of 15–30 mV depending on the recording conditions; and a \(-10\) fold increase in the amplitude of \(V_m\) fluctuations.

Model of high-frequency release

Computational models of cat neocortical pyramidal cells were used to estimate the release conditions and conductances necessary to account for these experimental measurements. A layer VI neocortical pyramidal cell (Fig. 2A) was reconstructed and incorporated in simulations (see METHODS). As both so-
matic and dendritic recordings are critical to constrain, the simulations of synaptic activity (see following text), passive responses from both types of recordings (Paré et al. 1997) were used to constrain the passive parameters of the model. The fitting was performed such that the same model could fit both somatic and dendritic recordings obtained in deep pyramidal cells in the absence of synaptic activity (TTX + synaptic blockers; see METHODS). The same model could fit both traces (Fig. 2A) with the following optimal passive parameters: $g_{\text{leak}} = 0.045$ mS cm$^{-2}$, $C_m = 1 \mu$F/cm$^2$, and $R_i = 250 \Omega$cm (see METHODS). Another fit was performed by forcing $R_i$ to 100 \Omega$cm ($C_m = 1 \mu$F/cm$^2$ and $g_{\text{leak}} = 0.039$ mS cm$^{-2}$). Although the latter set of values were not optimal, they were used to check for the dependence of the results on axial resistance. A passive fit also was performed with high membrane resistance, based on whole cell recordings (Pongracz et al. 1991; Spruston and Johnston 1992), and a somatic shunt due to electrode impalement. In this case, the parameters were as follows: 10 nS somatic shunt, $g_{\text{leak}} = 0.0155$ mS cm$^{-2}$, $C_m = 1 \mu$F/cm$^2$, and $R_i$ was of either 250 or 100 \Omega$cm. A nonuniform leak conductance, low in soma and a high in distal dendrites (Stuart and Spruston 1998), also was tested (see METHODS). No further effort was made to optimize passive parameters as models and experiments were based on different cellular morphologies. This fitting procedure ensured that the model had an $R_i$ and a time constant consistent with both somatic and dendritic recordings free of synaptic activity.

The next step was to simulate TTX-resistant miniature synaptic potentials occurring in the same neurons. These miniature events were characterized in somatic and dendritic intracellular recordings after microperfusion of TTX in vivo (Paré et al. 1997) (Fig. 2B, left). To simulate them, a plausible range of parameters was determined based on in vivo experimental constraints. Then, a search within this parameter range was performed to find an optimal set that was consistent with all constraints. These constraints were the densities of synapses in different regions of the cell, as derived from morphological studies of neocortical pyramidal cells (DeFelipe and Farinas 1992; Farinas and DeFelipe 1991a,b; Larkman 1991; Mungai 1967; White 1989) (see METHODS); the quantal conductance at AMPA and GABA_A synapses, as determined by whole cell recordings of neocortical neurons (Markram et al. 1997; Salin...
The optimal values found were a density of 20 GABAergic synapses and a narrow region was found to satisfy the above constraints. The distribution of miniature amplifications was measured in soma and dendrites (Na, K currents; and the change in potassium and K currents; same model as in Fig. 9A). The range of values indicate different combinations of release frequency (from 75 to 150% of optimal values). Miniature synaptic events were simulated by uncorrelated release events at low frequency (same model as in Fig. 2B). See text for more details.

Experimental values were measured in intracellularly recorded pyramidal neurons in vivo (Experiments). The average value ((V_m)) and standard deviation (σ_v) of the V_m are indicated, as well as the R_m change, during active periods and after TTX application. The values labeled “TTX” correspond to the layer VI pyramidal cell model where active periods were compared to the layer VI pyramidal cell model where active periods were simulated by correlated high-frequency release on glutamatergic and GABAergic receptors. The model is shown without voltage-dependent currents (passive; same model as in Fig. 3D) and with voltage-dependent currents distributed in soma and dendrites (Na⁺ and K⁺ currents; same model as in Fig. 9A).

The range of values indicate different combinations of release frequency (from 75 to 150% of optimal values). Miniature synaptic events were simulated by uncorrelated release events at low frequency (same model as in Fig. 2B). See text for more details.

and Prince 1996; Stert and Ear 1992); the value of σ_v during miniature events after TTX application in vivo (−0.4 mV for somatic recordings and 0.6–1.6 mV for dendritic recordings) (Pare et al. 1997); the change in R_m due to miniature events, as determined in vivo (−8–12% in soma and 30–50% in dendrites) (Pare et al. 1997); and the distribution of mini amplitudes and frequency, as obtained from in vivo somatic and dendritic recordings (Fig. 2B, insets).

An extensive search in this parameter range was performed and a narrow region was found to satisfy the above constraints. The optimal values found were a density of 20 GABAergic synapses per 100 μm² in the soma, 60 GABAergic synapses per 100 μm² in the initial segment, 10 GABAergic synapses and 60 glutamatergic (AMPA) synapses per 100 μm² in the dendrites; a rate of spontaneous release (assumed uniform for all synapses) of 0.009–0.012 Hz; and quantal conductances of 1,000–1,500 pS for glutamatergic and 400–800 pS for GABAergic synapses. In these conditions, simulated miniature events were consistent with experiments (Fig. 2B, right), with σ_v of 0.3–0.4 mV in soma and 0.7–1.4 mV in dendrites, and R_m changes of 8–11% in soma and 25–37% in dendrites.

To simulate the intense synaptic activity occurring during active periods, we hypothesized that miniature events and active periods are generated by the same population of synapses with different conditions of release for GABAergic and glutamatergic synapses. The preceding model of miniature events was used to simulate active periods by increasing the release frequency at all synaptic terminals. Poisson-distributed release was simulated with identical release frequency for all excitatory synapses (f_e) as well as for inhibitory synapses (f_i). The release frequencies f_e and f_i affected the R_m and average V_m ((V_m)) (Fig. 3A). These aspects were constrained by the following experimental measurements (see preceding section): the R_m change produced by TTX should be ~80%; the V_m should be around −80 mV without synaptic activity; the V_m should be about −65 mV during active periods (E_Cl = −75 mV); and the V_m should be around −51 mV during active periods recorded with chloride-filled electrodes (E_Cl = −55 mV). Here again an extensive search in this parameter space was performed, and several combinations of excitatory and inhibitory release frequencies could reproduce correct values for the R_m decreases and V_m differences between active periods and after TTX (Fig. 3A). The optimal values of release frequencies were f_e = 1 Hz (range 0.5–3 Hz) for excitatory synapses and f_i = 5.5 Hz (range 4–8 Hz) for inhibitory synapses.

An additional constraint was the large V_m fluctuations experimentally observed during active periods, as quantified by σ_v (see preceding section). As shown in Fig. 3B (□, ○, ●, △), increasing the release frequency of excitatory or inhibitory synapses produced the correct R_m changes but always gave too small values of σ_v. High release frequencies led to membrane fluctuations of small amplitude, due to the large number of summing random events (Fig. 3B4). Variations within 50–200% of the optimal value of different parameters, such as synapse densities, synaptic conductances, frequency of release, leak conductance, and axial resistance, could yield approximately correct R_m changes and correct V_m but failed to account for values of σ_v observed during active periods (Fig. 3C, X).

One additional assumption had to be made to reproduce V_m fluctuations comparable to those occurring in vivo. In the cortex, action potential-dependent release is clearly not independent at different synapses, as single axons usually establish several contacts in pyramidal cells (Markram et al. 1997; Thomson and Deuchars 1997). More importantly, the presence of oscillatory amplitude fluctuations in the EEG (Fig. 1, A and B) implies correlated activity in the network. A correlation therefore was included in the release of different synapses (see METHODS). For the sake of simplicity, the correlation was irrespective of the proximity of synapses on the dendritic tree and correlations were treated independently for excitatory and inhibitory synapses. Figure 3D shows simulations of random synaptic bombardment similar to Fig. 3B4 but using different correlation coefficients. The horizontal alignment of the open symbols in Fig. 3D5 shows that the degree of correlation had a negligible effect on the R_m because the same amount of inputs occurred on average. However, the degree of correlation affected the standard deviation of the signal. Several combinations of excitatory and inhibitory correlations, within the range of 0.05–0.1, gave rise to V_m fluctuations with comparable σ_v as those observed experimentally during active periods (Fig. 3D5; compare with Fig. 1F; see also Table 1). Introducing correlations among excitatory or inhibitory inputs alone showed that excitatory correlations were most effective in reproducing the V_m fluctuations (Fig. 3D5, △).

To check if these results were affected by voltage-dependent currents, we estimated the voltage-dependent currents present in cortical cells from their current-voltage (I-V) relationship. The I-V curve of a representative neocortical cell after TTX microperfusion is shown in Fig. 4A. The I-V curve was approximately linear at V_m±60 mV but displayed an important outward rectification at more depolarized potentials similar to in vitro observations (Stafstrom et al. 1982). The R_m was of ~57.3 MΩ at values around rest (about ~75 mV) and 30.3 MΩ at more depolarized V_m (greater than ~60 mV), which represents a relative R_m change of 47%. This cell had the strongest outward rectification in six cells measured after TTX (relative R_m change of 30 ± 11%, n = 6).
In the model, this type of $I-V$ relation was simulated by including two voltage-dependent K currents, $I_{Kd}$ and $I_M$ (see METHODS). In the presence of these two currents, the model displayed a comparable rectification as the cell showing the strongest rectification in experiments under TTX (Fig. 4B; the straight lines indicate the same linear fits as in A for comparison).

The constraining procedure described above then was used to estimate the release conditions in the presence of voltage-dependent currents. First, the model including $I_{Kd}$ and $I_M$ was fit to passive traces obtained in the absence of synaptic activity to estimate the leak conductance and leak reversal (similar to Fig. 2A). Second, the release rate required to account for the $\sigma_v$...
and $R_{in}$ change produced by miniature events was estimated as in Fig. 2B. Third, we estimated the release rates that could best reproduce the $R_{in}$, $(V_m)$ and $\sigma_v$ (see Fig. 3).

The presence of voltage-dependent currents produced small—but detectable—changes in the optimal release conditions. For example, the same $R_{in}$ change, $(V_m)$ and $\sigma_v$ as the passive model with $f$ = 1 Hz and $f_i$ = 5.5 Hz was obtained with $f_e$ = 0.92 Hz and $f_i$ = 5.0 Hz (8–9% lower) in a model containing $I_{K_d}$ and $I_M$. Both models gave nearly identical $\sigma_v$ values for the same value of correlation. A similar constraining procedure also was performed using a nonuniform leak distribution with high leak conductances in distal dendrites (see Methods), in addition to $I_{K_d}$ and $I_M$, and nearly identical results were obtained (not shown). We therefore conclude that leak and voltage-dependent $K^+$ currents have a small contribution to the $R_{in}$ and $\sigma_v$ of active periods, which are mostly determined by synaptic activity.

Impact of synaptic activity on integrative properties

The experimental evidence for a $\approx$80% decrease in $R_{in}$ due to synaptic bombardment betrays a massive opening of ion channels. In the model, the total conductance due to synaptic activity was 7–10 times larger than the leak conductance. In conditions of high membrane resistance based on whole cell recordings (Pongracz et al. 1991; Spruston and Johnston 1992), the conductance due to synaptic activity was 20–30 times larger than the dendritic leak conductance.

The impact of this massive increase in conductance on dendritic attenuation was investigated by comparing the effect of current injection in active periods and synaptic quiescence (Fig. 5). In the absence of synaptic activity (Fig. 5B, smooth traces), somatic current injection (Fig. 5B, left) elicited large voltage responses in dendrites, and reciprocally (Fig. 5B, right), showing a moderate electrotonic attenuation. By contrast, during simulated active periods (Fig. 5B, noisy traces), voltage responses to identical current injections were reduced markedly, betraying a greatly enhanced electrotonic attenuation. In these conditions, the relative amplitude of the deflection induced by the same amount of current with and without synaptic activity, as well as the difference in time constant, were in agreement with experimental observations (compare Fig. 5B, Soma, with Fig. 1, C and D). The effect of synaptic bombardment on the time constant was also in agreement with previous models (Bernander et al. 1991; Holmes and Woody 1989; Koch et al. 1996).

Dendritic attenuation was characterized further by computing somatodendritic profiles of $V_m$ with steady current injection in the soma: in the absence of synaptic activity (Fig. 5C, Quiet), the decay of $V_m$ after somatic current injection was characterized by space constants of 515–930 $\mu$m, depending on the dendritic branch considered, whereas the space constant was reduced by about fivefold (105–181 $\mu$m) during simulated active periods (Fig. 5C, Active).

To estimate the convergence of synaptic inputs necessary to evoke a significant somatic depolarization during active periods, a constant density of excitatory synapses was stimulated synchronously in “proximal” and “distal” regions of dendrites (as indicated in Fig. 6A). In the absence of synaptic activity, simulated EPSPs had large amplitudes (12.6 mV for proximal and 6.0 mV for distal; Fig. 6B, Quiet). By contrast, during simulated active periods, the same stimuli gave rise to EPSPs that were barely distinguishable from spontaneous $V_m$ fluctuations (Fig. 6B, Active). The average EPSP amplitude was 5.4 mV for proximal and 1.16 mV for distal stimuli (Fig. 6B, Active, avg), showing that EPSPs are attenuated by a factor of 2.3–5.2 in this case, with the maximal attenuation occurring for distal EPSPs. Figure 6C shows the effect of increasing the number of synchronously activated synapses. In quiescent conditions, <50 synapses on basal dendrites were sufficient to evoke a 10-mV depolarization at the soma (Quiet, proximal), and the activation of $\approx$100 distal synapses was needed to achieve a similar depolarization (Quiet, distal). During simulated active periods, >100 basal dendritic synapses were nec-
necessary to reliably evoke a 10-mV somatic depolarization (Active, proximal), whereas the synchronous excitation of ≤415 distal synapses only evoked depolarization of a few millivolts (Active, distal).

To determine whether these results are dependent on the specific morphology of the studied cell, four different cellular geometries were compared, ranging from small layer II–III cells to large layer V pyramidal cells (Fig. 7A). In experiments,
the absolute $R_{in}$ values varied from cell to cell. However, the relative $R_{in}$ change produced by TTX was similar in all cells recorded. Similarly, in the model, the absolute $R_{in}$ values depended on the cellular geometry: using identical passive parameters, the $R_{in}$ values of the four neurons shown in Fig. 7A ranged from 23 to 94 MΩ. However, high-frequency release conditions had a similar impact on their membrane properties. Using identical synaptic densities, synaptic conductances, and release conditions as detailed above led to a decrease in $R_{in}$ of $\sim 80\%$ for all cells (Fig. 7B). $V_{m}$ fluctuations also depended critically on the degree of correlation between the release of different synapses. Uncorrelated events produced too small $\sigma_v$ (Fig. 7B, ×), whereas a correlation of 0.1 could reproduce both the $R_{in}$ change and $\sigma_v$ (Fig. 7B, △). The value of $\sigma_v$ was correlated with cell size (not shown), and the variability of $\sigma_v$ values was relatively high compared with that of $R_{in}$ decreases. The effect of synaptic activity on dendritic attenuation was also independent of the cell geometry: the space constant was reduced by about fivefold in all four cells (not shown). Moreover, for the two layer V neurons, stimulating several hundreds of synapses at a distance of $>800$ μm from the soma had undetectable effects during active periods (Fig. 7C). This result was also reproduced using low axial resistivities (Fig. 7C, dashed lines).

These results show that intense synaptic activity has a drastic effect on the attenuation of distal synaptic inputs. However, voltage-dependent currents in dendrites may amplify EPSPs (Cook and Johnston 1997) or trigger dendritic spikes that propagate toward the soma (Stuart et al. 1997). Therefore the attenuation of EPSPs must be reexamined in models that include active dendritic currents.

**Firing properties during active periods**

The response of the simulated neuron to depolarizing current pulses was tested in the presence of voltage-dependent Na$^+$ currents, in addition to $I_{Kd}$ and $I_{M}$. In the absence of synaptic activity (Fig. 8A), the model displayed pronounced spike frequency adaptation due to $I_{Kd}$, similar to “regular spiking” pyramidical cells in vitro (Connors et al. 1982). However, spike frequency adaptation was not apparent in the presence of correlated synaptic activity (Fig. 8B), probably due to the very small conductance of $I_{M}$ compared with synaptic conductances. Nevertheless, the presence of $I_{M}$ affected the firing behavior of the cell, as suppressing this current enhanced the excitability of the cell (Fig. 8B, No $I_{M}$). This is consistent with the increase of excitability demonstrated in neocortical slices (McCormick and Prince 1986) after suppression of $I_{M}$ by application of acetylcholine.

In the presence of Na$^+$ and K$^+$ voltage-dependent currents, simulated active periods generated “spontaneous” firing at an average rate that depended on the action potential threshold, which was affected by Na$^+$ current densities. Setting the threshold at about $-55$ mV in soma, based on our experiments, led to a sustained firing rate of $\sim 10$ Hz (Fig. 9A), with all other features consistent with the model described earlier. In particular, the $R_{in}$ reductions and values...
of \( \sigma_c \) produced by synaptic activity were affected minimally by the presence of voltage-dependent currents (Table 1). However, this was only valid for \( R_m \) calculated in the linear region of the I-V relation (less than \(-60 \text{ mV}\); see Fig. 4). Thus at \( V_m \) more negative than \(-60 \text{ mV}\), the membrane parameters are essentially determined by background synaptic currents with a minimal contribution from intrinsic voltage-dependent currents.

In these conditions, the firing rate of the cell was sensitive to the release frequency: a threefold increase in release frequencies led to a proportional increase in firing rate (from \(-10 \text{ to } -30 \text{ Hz}\); Fig. 9B, - - -). Indeed, if all release frequencies were increased by a given factor, the firing rate increased by about the same factor (Fig. 9C, □). This shows that, within this range of release frequencies, the average firing rate of the cell reflects the average firing rate of its afferents. However, this relationship was broken if the release frequency was changed only at excitatory synapses: doubling the excitatory release frequency with no change in inhibition tripled the firing rate (Fig. 9C, ●).

Surprisingly, in Fig. 9B there was only a 12% \( R_m \) difference between the 10 and 30 Hz conditions, although the release frequency was threefold higher. This is due to the saturation effect of the \( R_m \) change as a function of release frequency (Fig. 3A1). This property may explain the observation that visually evoked responses are not paralleled by substantial \( R_m \) changes in area 17 neurons (Berman et al. 1991).

Sharp events of lower amplitude than action potentials are also visible in Fig. 9, A and B. These events are likely to be dendritic spikes that did not reach action potential threshold in the soma/axon region, similar to the fast prepotentials described by Spencer and Kandel (1961). Similar events were reported in intracellular recordings of neocortical pyramidal cells in vivo (Deschénes 1981).

**Integrative properties during active periods**

The dendritic attenuation of EPSPs was examined in the presence of voltage-dependent Na\(^+\) and K\(^+\) dendritic conductances. Using the same stimulation paradigm as in Fig. 6B, proximal or distal synapses reliably fired the model cell in quiescent conditions (Fig. 10A, Quiet). The stimulation of distal synapses elicited dendritic action potentials that propagated toward the soma in agreement with a previous model (Paré et al. 1998a). During active periods (Fig. 10A, Active), proximal or distal stimuli did not trigger spikes reliably although the clustering of action potentials near the time of the stimulation (*) shows that EPSPs affected the firing probability. The evoked response, averaged from 1,000 sweeps under intense synaptic activity (Fig. 10A, Active, avg), showed similar amplitude for proximal or distal inputs. Average responses did not reveal any spiky waveform, indicating that action potentials were not precisely timed with the EPSP in both cases.

It is interesting to note that, in Fig. 10A, distal stimuli evoked action potential clustering, whereas proximal stimuli did not, despite the fact that a larger number of proximal synapses were activated. Distal stimuli evoked dendritic action potentials, some of which reached the soma and led to the observed cluster. Increasing the number of simultaneously activated excitatory synapses enhanced spike clustering for both proximal and distal stimuli (Fig. 10B, *). This also was evidenced by the spiky components in the average EPSP (Fig. 10B, Active, avg). Comparison of responses evoked by different numbers of activated synapses (Fig. 10C) shows that the convergence of several hundred excitatory synapses was necessary to evoke spikes reliably during intense synaptic activity. It is remarkable that with active dendrites, similar conditions of convergence were required for proximal or distal inputs, in sharp contrast to the case with passive dendrites, in which there was a marked difference between proximal and distal inputs (Fig. 6C).

The magnitude of the currents active at rest may influence these results. In particular, the significant rectification present at levels more depolarized than \(-60 \text{ mV}\) (Fig. 4A) may affect the attenuation of depolarizing events. To investigate this aspect, we estimated the conditions of synaptic convergence using different distributions of leak conductances. Although suppressing the \( I_m \) conductance enhanced the excitability of the cell (see preceding text), it did not affect the convergence requirements in conditions of intense synaptic activity. It is not possible to evoke spikes reliably during intense synaptic activity by supressing the \( I_m \) conductance enhanced the excitability of the cell (see preceding text), it did not affect the convergence requirements in conditions of intense synaptic activity. It is not possible to evoke spikes reliably during intense synaptic activity by suppressing the \( I_m \) conductance enhanced the excitability of the cell (see preceding text), it did not affect the convergence requirements in conditions of intense synaptic activity. It is not possible to evoke spikes reliably during intense synaptic activity.
The present study provides the first quantitative characterization of the membrane properties of neocortical pyramidal cells in conditions of network activity similar to those observed during the waking state. Intracellular recordings and biophysical models indicated that synaptic activity produces a massive conductance change that is about five times larger than the conductances already present in the cell in the absence of synaptic activity. The model shows that this conductance increase has a major impact on the electrotonic attenuation of EPSPs along the dendritic tree. As this finding might have important implications for understanding how cortical cells process information, we first consider possible pitfalls of our experimental and modeling procedures and then discuss the significance of these findings.

**Possible sources of error**

A first possible source of error is that the ∼80% decrease in $R_{in}$ produced by synaptic activity was observed under anesthesia and a different value might characterize the waking brain. However, the fact that cells fire at similar rates during active periods of ketamine-xylazine anesthesia and during wakefulness indicates that both must be characterized by a similar pattern of synaptic bombardment. This view also is supported by the similar spectral composition of the EEG in these two states.

Two factors might have led us to underestimate the decrease in $R_{in}$ produced by spontaneous synaptic activity. First, NMDA receptors are antagonized by ketamine, and these channels must reduce further the $R_{in}$ of cortical cells during the waking state. Second, TTX microperfusion may not have been completely effective in blocking all synapses (although evoked EPSPs were suppressed) (Paré et al. 1997, 1998b), therefore contributing to an additional underestimation of the real $R_{in}$ change. Ideally, the same analysis should be performed in awake animals, which raises a number of technical difficulties.

Another possible source of error is that the contribution of neuromodulatory currents to the $R_{in}$ change was not investigated. Most likely, TTX application not only suppresses fast (ionotropic) synaptic activity but also neuromodulatory (metabotropic) influences. Future studies should address this aspect using microperfusion of ionotropic synaptic blockers (NBQX, 2-amino-5-phosphonopentanoic acid, and bicuculline) to estimate the respective contribution of ionotropic and metabotropic activity to the $R_{in}$ change.

A source of error often raised for sharp-electrode recordings is that the impalement damages the cell. Experimental and modeling evidence suggests that cell damage had a negligible effect on the relative $R_{in}$ changes measured experimentally. First, blocking spontaneous synaptic activity in vivo using TTX leads to $R_{in}$ values that are similar to those seen in vitro using the same type of electrodes (Paré et al. 1998b). Second, we report here low $R_{in}$ values during intense synaptic activity and much larger $R_{in}$ values after TTX application. These data clearly show that the low $R_{in}$ of neocortical cells in vivo is not due to cell damage but is attributable to action potential-dependent factors. The marked difference in $V_m$ before and after TTX also shows that the depolarized $V_m$ of neocortical cells in vivo is also a consequence of synaptic activity.

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**DISCUSSION**

Possible sources of error

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The model supports these conclusions by showing that synaptic activity can account for the changes in $R_{in}$, $V_m$, and $s_v$. Given that the change in $R_{in}$ attributable to synaptic activity was estimated experimentally in the same cells before and after TTX, it is reasonable to assume that the same electrode shunt was present in both conditions. This shunt was included implicitly in the model when adjusting its passive properties (Fig. 2A). It also was included explicitly in the model, in combination with higher membrane resistivity, and similar results were obtained. Given that dendritic attenuation is determined essentially by dendritically located conductances, it is not surprising that a simulated electrode shunt in the soma had a minimal effect here.

Another possible source of error is the contribution of voltage-dependent currents that are activated indirectly by synaptic events. In pyramidal neurons, the most numerous ion channels are synaptic: in hippocampal pyramidal cell’s dendrites, Na$^+$ and K$^+$ currents total $\sim$100–200 pS/μm$^2$ (Magee and Johnston 1995; Magee et al. 1998) while AMPA receptors amount to $\sim$700 pS/μm$^2$ (assuming 0.6 spines per μm$^2$, 1 release site per spine and a quantal conductance of 1,200 pS). The present analysis was based on relatively hyperpolarized $V_m$ (less than $-55$ mV), as cells were around $-80$ mV under TTX and in the range of $-70$ to $-55$ mV during active periods, with rare excursions above $-55$ mV (see Fig. 1F). In this range of membrane potential, only a small fraction of voltage-dependent channels should be open, whereas a large fraction of ionotropic receptor channels seem to be activated in the conditions studied here. The current-voltage relation was indeed approximately linear in the $V_m$ range below $-60$ mV (Fig. 4A), suggesting that the $R_{in}$ change estimated in this region of $V_m$ is essentially due to synaptic currents. In addition, simulations indicate that voltage-dependent K$^+$ currents contribute $<$10% of the measured $R_{in}$ change, even though the model was fit to the cell showing the strongest rectification in our database (Fig. 4). Nevertheless, a significant rectification is present at levels more depolarized than $-55$ mV (Fig. 4A) and should affect the attenuation of depolarizing events. Together, these data indicate that, for $V_m$s lower than $-60$ mV, the conductance due to synaptic activity accounts for most of the $R_{in}$ change observed. Further models and experiments are required to investigate if these conclusions are also valid for neurons possessing a prominent $I_h$. (Stuart and Spruston).
densities, reversal potential, rate of release, correlation of release, as well as the nature, distribution, and kinetics of voltage-dependent currents. These different possibilities should be addressed by future studies as data become available. Second, the axial resistance $R_i$ could not be constrained. This parameter is usually estimated in the range of 200–300 $\Omega \text{cm}$ (Rall et al. 1992), but a recent study suggested lower values (Stuart and Spruston 1998). We have tried simulations using $R_i$ of 250 or 1000$\Omega \text{cm}$ and nearly identical results were obtained (Figs. 7C and 11C).

A final source of error is that the models were not simulating the cellular geometries of the recorded neurons. The fact that similar results were obtained using different cellular geometries (Fig. 7) indicates that the exact dendritic morphology was not critical here. However, the dendritic morphology influenced the value of $\sigma_i$ for equivalent changes in $R_i$ (Fig. 7B). Future studies should use cellular reconstructions of the recorded cells, allowing more precise simulations of passive properties and of the impact of synaptic currents.

Release conditions at cortical synapses

In the suprasylvian cortex of awake cats, neurons display ‘‘idle’’ firing rates of $\sim 10$ Hz but the rate increases to 20–60 Hz when cells respond to sensory stimuli (Kalaska 1996). In the model, a $\sim 10$-Hz firing rate was obtained with release frequencies of 0.5–3 Hz for excitatory synapses and 4–8 Hz for inhibitory synapses. These values are significantly below the reported average firing rate of cortical neurons in this state, suggesting that the release probability of excitatory synapses is significantly less than unity (0.025–0.6). Indeed, in vitro studies indicate a significant decrease in release probability at steady state (Thomson et al. 1993). It should be noted, however, that the estimation of release frequency is dependent on the synaptic density: a twice lower density would require a doubled release frequency to reproduce equivalent results. The present densities were matching the density of spines in rat neocortical dendrites (0.6 spine per $\mu^2$ in Larkman 1991). It is possible that the spine density is lower or higher in cats in which case our estimates of release probability should be revised.

Nevertheless, these release conditions could reproduce the depolarized $V_n$ and the reduced $R_{in}$ evidenced by in vivo experiments. This seemed independent of the exact details of dendritic morphology and cell size (Fig. 7), suggesting that different cells in the neocortex experience similar release conditions during active periods. The model therefore predicts that these changes are generic and are typical of the state of cortical neurons during intense network activity.

In addition to high-frequency release conditions, it was necessary to include a significant correlation among release events to account for experimental measurements. No correlation was necessary to reproduce the characteristics of miniature synaptic potentials, as expected if these events arise from spontaneous release occurring independently at each terminal. On the other hand, an average correlation of $\sim 0.1$ was necessary to account for the $V_n$ fluctuations observed during active periods. This is consistent with the average correlation of 0.12 measured between pairs of neurons in the cerebral cortex of behaving monkeys (Zohary et al. 1994). The model suggests that this factor, together with the high-frequency release con-
ditions, is sufficient to account for the membrane properties of neocortical cells during active periods. Our results are compatible with the view that during active periods, neocortical cells display weakly correlated discharges (c ~ 0.1) (Zohary et al. 1994) occurring at high firing rates (~5–20 Hz) (Evarts 1964; Hubel 1959; Steriade 1978).

Implication for dendritic integration

According to cable theory (Rall 1995), dendritic attenuation depends on the membrane conductance. Because our experiments provide evidence for a massive increase of the total membrane conductance during active periods, they predict a major effect on dendritic attenuation, but the exact magnitude of this effect is unknown. The model, constrained by $R_{in}$, $V_{m0}$, and $\sigma_1$ before and after TTX, revealed drastic effects on dendritic attenuation and that a large number of convergent dendritic synaptic inputs are required to affect the voltage at the soma. By simulating synchronous excitatory synaptic events, it was estimated that the synchronous activation of 80–150 synapses on basal dendrites was necessary for the cell to reach action potential threshold (~55 mV), whereas ≤415 synapses simulated in distal branches evoked insufficient somatic depolarization (Fig. 6C) or no depolarization at all (Fig. 7C). These simulations show that, because of passive dendritic attenuation, it is difficult for EPSPs arising at distal sites to have a significant effect on the soma if passive properties had to be considered solely.

A very different picture was seen in the presence of dendritic Na$^+$ and K$^+$ currents. During intense background synaptic activity, the convergence of hundreds of coincident synaptic inputs was required to evoke spiking reliably (Fig. 10, A–C), similar to the convergence requirements determined with passive dendrites (Fig. 6). However, by contrast with the tremendous attenuation of distal inputs in a passive neuron (Fig. 7C), with active dendrites, the number of synapses required to evoke spiking reliably was approximately the same for proximal and distal stimulation (Fig. 10C). This shows that integrative properties cannot be simply deduced from passive dendritic attenuation. Low-amplitude EPSPs experienced tremendous attenuation because they were subthreshold for the activation of voltage-dependent currents. However, the synchronized stimulation of hundreds of excitatory synapses evoked dendritic action potentials that propagated toward the soma and had an equivalent effect on the firing probability irrespective of their distance from the soma. Active dendrites therefore diminish the variability of the response due to the location of inputs, in agreement with a previous proposition (Cook and Johnston 1997).

The fact that a large number of synchronous synaptic events are required to evoke spiking reliably could suggest that pyramidal cells act like coincidence detectors, as proposed previously (Bernander et al. 1991). However, Fig. 9B also shows that the cell reliably responds to the average firing rate of its afferents. Therefore our experiments and models cannot distinguish between these two possibilities. Rather, our results suggest that, in conditions of intense synaptic activity, pyramidal cells respond reliably only when a very large number of synapses change their release frequency or timing, therefore detecting changes in large populations of neurons.

Predictions

The first prediction of this model is that neurons intracellularly recorded in the suprasylvian cortex during the awake state should have markedly reduced $R_{in}$ (by a ≥5-fold factor, see preceding text). This could be tested by performing intracellular recordings in awake animals together with local application of TTX. Although these experiments presently represent a real technical challenge, it is likely that improvements in intracellular recording techniques will make it feasible in the near future.

The second prediction is that a large number of synapses must be activated to influence significantly the probability of action potential generation in neocortical pyramidal neurons in active states. This could be tested using intracellular recordings in ketamine-xyazine anesthesia in a first step and subsequently in awake animals if possible. The convergence criteria could be estimated by using local iontophoresis of increasing amounts of glutamate. The effect on action potentials could be evaluated using similar averaging procedures as shown here. Performing the same experiment under TTX may be used to provide a control of the amplitude/conductance of the evoked EPSPs in the absence of synaptic activity.

The third prediction of the model is that during active periods, similar convergence criteria should be observed for the activation of proximal versus distal synapses. This could be tested using similar paradigms as above by comparing the effect of local glutamate application in deep versus superficial layers of the cortex. The threshold amount of glutamate should be independent of the depth of application.

In conclusion, experiments and models indicate that intense network activity similar to the waking state consists in weakly correlated high-frequency release conditions responsible for a major increase of conductance in pyramidal neurons. The model further indicates that hundreds of highly correlated inputs are required to discharge the cell reliably (Fig. 10C). We suggest that intense network activity maintains pyramidal cells in an idle state during which they are ready to respond rapidly to brief changes of correlation within hundreds of their synaptic inputs. A change of correlation, or synchrony, seems to be the most efficient manner to carry information in these conditions, which supports a possible role for synchronized oscillations in cortical information processing.

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