Synaptic Enhancement Induced Through Callosal Pathways in Cat Association Cortex

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INTRODUCTION

Most investigations on synaptic plasticity have been carried out in the hippocampus (reviewed in Bear and Malenka 1994; Malenka and Nicoll 1993). Although these processes seemingly affect neocortical neurons, some forms of synaptic plasticity have also been reported in neocortex, both in vitro (Aroniadou and Keller 1995; Artola and Singer 1987; Bear and Kirkwood 1993; Kimura et al. 1989; Sjöström et al. 2003) and in vivo (Keller et al. 1991; reviewed in Tsumoto 1992). The interest for synaptic plasticity is due to the belief that long- and short-term potentiation are among the best candidates toward the understanding of mechanisms through which memories are formed and stored in the mammalian brain.

Previous studies have shown that low-frequency (5–15 Hz) stimulation produces short-term synaptic plasticity in thalamocortical pathways (Castro-Alamancos and Connors 1996; Steriade et al. 1998b). The callosal pathway is implicated in the synchronization of various cortically generated rhythms and oscillatory activities during states of waking and sleep, and may play an important role in the induction of synaptic plasticity (Steriade 2003; Steriade and Timofeev 2003). We have previously shown that homosynaptic potentiation of responses in callosal pathways can be obtained by stimulating at the frequency of 10 Hz, even in animals with extensive thalamic lesions (Nuñez et al. 1993; Steriade et al. 1993). In those experiments, only 10-Hz stimulation was used, only intrinsically bursting (IB) neurons were recorded, and the duration of potentiation was not measured.

In this study, we applied single pulses to callosal pathway to evoke control excitatory postsynaptic potential (EPSP) responses that were followed by rhythmic pulse-trains at different frequencies, representing the conditioning stimulation; thereafter, single pulses were applied again to test changes in synaptic responses by comparing the amplitudes of control and conditioned EPSPs. With all frequencies used, we found increased amplitudes of conditioned EPSPs compared with control; the enhancement of test EPSPs evoked by single pulses lasted for about 5–30 min in animals under barbiturate anesthesia. To test the possibility that this EPSPs’ potentiation may be dependent on N-methyl-D-aspartate (NMDA) receptors at callosal synapses (Kumar and Huguenard 2001), we performed microdialysis with an NMDA receptor blocker in barbiturate-treated animals, made recordings in animals under ketamine-xylazine anesthesia (which blocks NMDA receptors), and found that NMDA blockade significantly reduces EPSPs’ potentiation.

METHODS

Animal preparation

Experiments were conducted on 33 adult cats under barbiturate anesthesia (pentobarbital sodium, 35 mg/kg, ip) and 10 adult cats under ketamine-xylazine anesthesia (10–15 and 2–3 mg/kg, im, respectively). The animals were paralyzed with gallamine triethiodide after the EEG showed typical signs of deep general anesthesia, essentially consisting of sequences of spindle waves (7–14 Hz) under barbiturate anesthesia and slow oscillation (0.5–1 Hz) under ketamine-xylazine anesthesia. Supplementary doses of anesthetics were administered at the slightest changes toward activated EEG patterns. The cats were ventilated artificially with the control of end-tidal CO₂ at 3.5–3.7%. The body temperature was maintained at 37–38°C, and the heart rate was ~90–100 beats/min. Stability of intracellular recordings was ensured by the drainage of cisterna magna, hip suspension, bilateral pneumothorax, and filling the hole made for recordings with a solution of 4% agar.

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Cissé, Youssouf, Sylvain Crochet, Igor Timofeev, and Mircea Steriade. Synaptic enhancement induced through callosal pathways in cat association cortex. J Neurophysiol 92: 3221–3232, 2004. doi:10.1152/jn.00537.2004. The corpus callosum plays a major role in synchronizing neocortical activities in the two hemispheres. We investigated the changes in callosally elicited excitatory postsynaptic potentials (EPSPs) of neurons from cortical association areas 5 and 7 of cats under barbiturate or ketamine-xylazine anesthesia. Single pulses to callosal pathway evoked control EPSPs; pulse-trains were subsequently applied at different frequencies to homotopic sites in the contralateral cortex, as conditioning stimulation; thereafter, the single pulses were applied again to test changes in synaptic responsiveness by comparing the amplitudes of control and conditioned EPSPs. In 41 of 42 neurons recorded under barbiturate anesthesia, all frequencies of conditioning callosal stimuli induced short-term (5–30 min) enhancement of test EPSPs elicited by single stimuli. Neurons tested with successive conditioning pulse-trains at different frequencies displayed stronger enhancement with high-frequency (40–100 Hz) than with low-frequency (10–20 Hz) rhythmic pulse-trains; >100 Hz, the potentiation saturated. In a neuronal sample, microdialysis of an N-methyl-D-aspartate (NMDA) receptor blocker in barbiturate-treated cats suppressed this potentiation, and potentiation of callosally evoked EPSPs was not detected in neurons recorded under ketamine-xylazine anesthesia, thus indicating that EPSPs’ potentiation implicates, at least partially, NMDA receptors. These data suggest that callosal activities occurring within low-frequency and fast-frequency oscillations play a role in cortical synaptic plasticity.

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Recordings and stimulation

Intracellular recordings from left suprasylvian association areas 5 and 7 were performed using glass micropipettes filled with a solution of 3 M potassium-acetate (KAc). A high-impedance amplifier with active bridge circuitry was used to record the membrane potential ($V_m$) and inject current into the neurons. Field potentials were recorded in the vicinity of impaled neurons, using bipolar coaxial electrodes, with the ring (pial surface) and the tip (cortical depth) separated by 0.8 – 1 mm.

Stimulating electrodes were inserted in homotopic points of the contralateral (right) areas 5 and 7 (Fig. 1A). We used low-intensity (0.02 – 0.5 mA) and short-duration (0.05 – 0.2 ms) stimuli, which were preserved for the same neuron throughout the experiment. The amplitude of EPSPs was measured from the baseline (1 ms before stimulus artifact) to the peak of EPSPs to avoid multisynaptic responses that may be contained after the initial slope of the EPSP.

Electrical stimulation was applied every 2 or 3 s to the callosal pathway to evoke control EPSPs (1 – 4 min). Thereafter, 8 – 15 pulse-trains were applied as conditioning stimulation. Each pulse-train consisted of 10 pulses and lasted for 0.1 – 1 s (depending on the frequency used), and the interpulse-trains were separated by 2 or 3 s.

Microdialysis

To assess the involvement of NMDA receptors in the callosal-induced potentiation, the NMDA receptor blocker d(-)-2-amino-5-phosphonopentanoic acid (AP-5, Tocris), was applied locally using reverse microdialysis technique. The membrane of the microdialysis probe (membrane: 2 mm length, 0.22 mm diam; EICOM) was inserted in the cortex, and the recording micropipettes were placed at 0.2 – 0.3 mm from the membrane. The microdialysis probe was perfused either with artificial cerebrospinal fluid (ACSF, concentration in mM: 124 NaCl, 2.5 KCl, 26 NaHCO$_3$, 1.25 Na$_2$HPO$_4$, 2 MgSO$_4$, 1 MgCl$_2$, and 1 CaCl$_2$) or with a solution of AP-5 (1 mM) dissolved in ACSF. The concentration of AP-5 in the cortex is expected to reach 10% of the concentration in the perfused solution (100 μM) (Juhasz et al. 1989; Quan and Blatteis 1989). The changes in callosally evoked EPSPs after application of pulse-trains at 40 Hz were tested during the perfusion of ACSF only, during the application of AP-5, and 20 – 30 min after washout with ACSF in the same neurons.

At the end of experiments, the cats were given a lethal dose of pentobarbital (50 mg/kg, iv). The experimental procedures were approved by the committee for animal care of Laval University and were performed according to National Institutes of Health guiding principles.
RESULTS

First, we present the database and document the stability of membrane potential ($V_m$) and tested EPSPs induced by callosal stimulation during the long periods required for the analysis of their changes following conditioning callosal stimulation with different frequencies. Next, data resulting from application of conditioning pulse-trains from relatively low (10–20 Hz) to higher (40–100 Hz) frequencies are presented, and we compare the effects exerted on test EPSPs of the same neuron by low- and high-frequency conditioning stimulation in animals under barbiturate anesthesia. Then, we present data with application of rhythmic conditioning pulse-trains in incremental and decremental ways, i.e., from low (10 Hz) to highest frequencies (≤500 Hz) and vice versa. Finally, we present the results obtained using microdialysis of AP-5 in barbiturate-treated animals as well as the data collected in animals under ketamine-xylazine anesthesia.

Database and stability of long-term recordings

Of >170 neurons recorded intracellularly in areas 5 and 7, we retained 42 neurons for analysis that could be recorded for periods of time from 20 to 120 min under barbiturate anesthesia, with resting $V_m$ (without current) of $-72 \pm 0.9$ (SE) mV and $V_m$ fluctuations that did not exceed 1–2 mV. Of those 42 neurons, 34 were regular-spiking (RS), 5 were fast-rhythmic-bursting (FRB), and 3 were IB, as characterized by responses to depolarizing current pulses (see Steriade 2001). In addition, seven RS neurons could be recorded before and after AP-5 microdialysis. Ten other neurons were recorded under ketamine-xylazine anesthesia.

Under barbiturate anesthesia, we tested 23 neurons with single conditioning pulse-trains (10, 20, 30, 40, 50, and 100 Hz) and 19 neurons with two or more conditioning pulse-trains. Under ketamine-xylazine anesthesia, we tested three neurons with single conditioning pulse-trains (10 and 50 Hz) and seven neurons with two or more conditioning pulse-trains (10, 40, and 100 Hz).

Neurons responsive to contralateral cortical stimulation (Fig. 1A) were located at depths between 0.3 and 1.5 mm. This wide distribution corroborates earlier morphological and physiological studies showing that callosal projecting and receiving neurons of cats and ferrets are located not only in layers 2/3 but also in infragranular layers (Barbaresi et al. 1994; Innocenti 1986; Innocenti et al. 2002). The peculiar amplitude and latency of callosally evoked responses in FRB neurons, which display EPSPs whose amplitudes are two- to threefold larger, and latencies two- to threefold shorter, than in other neuronal classes (Cissé et al. 2003), were also observed in these experiments. Thus the control EPSPs in the FRB neuron depicted in Fig. 2B had an amplitude of ~10–12 mV and a latency of 1.4 ms compared with lower amplitudes and longer latencies of control EPSPs in other neuronal classes.

The technical procedures employed to obtain stable intracellular recordings, described in METHODS, allowed long-term recordings without significant changes in $V_m$ as well as in amplitudes and latencies of test EPSPs. The $V_m$ stability is critical in studies of synaptic plasticity because the responsiveness of neurons is strongly affected by large $V_m$ fluctuations. The stability of recordings is shown in Fig. 1, B and C, with two RS neurons, showing that the $V_m$ was stable, and callosally evoked EPSPs, sometimes followed by prolonged hyperpolarizations, preserved the same amplitudes over periods from 20 to 55 min. Similar aspects resulted from all 40 analyzed neurons from areas 5 and 7. The rather long latencies of some callosally evoked EPSPs (~5 ms in Fig. 2A; ~6 ms in Fig. 3) do not necessarily indicate that di- or polysynaptic pathways are involved, since there was no jitter in the onset latency for EPSPs activated from the contralateral cortex, the EPSPs could follow high frequencies of stimulation, and the latencies for antidromic invasion in this pathway can be as long as 18 ms (Cissé et al. 2003). However, we acknowledge that callosally evoked EPSPs may be mediated by a mixture of callosal projections and intracortical collaterals of callosally projecting neurons. To avoid responses evoked via di- or multisynaptic pathways, we mainly analyzed the monosynaptic EPSPs, as reflected in the initial slope of these responses, and did not analyze the events that followed the peak of the initial slope (see Fig. 2B).

The pulse-trains used as conditioning stimulation were applied through the same electrode, whereas various neurons were recorded along the same micropipette track. Although stimulus trains were not always delivered to a naïve region of the contralateral cortex, residual facilitation cannot account for the results because, before any conditioning-testing trials, control EPSPs were recorded for long periods of time to assess the stability of recordings. More importantly, we obtained evidence that neurons recorded for the first time during experiments displayed similar potentiation as other neurons (Fig. 6, A and B).

Potentiation of callosally evoked EPSPs by low- and high-frequency stimulation under barbiturate anesthesia

Single electrical volleys were applied every 2 or 3 s to the callosal pathway to evoke control EPSPs (minimum 20). They were followed by 8–15 pulse-trains, lasting for 0.2–1 s (depending on the frequency used), separated by 2 or 3 s, delivered at frequencies of 10–20 Hz (Fig. 2A) or higher frequencies, 40–100 Hz (Fig. 2B), which represented the conditioning stimulation. Thereafter, single pulses were applied again to test synaptic changes by comparing the amplitudes of control and conditioned EPSPs. In some neurons ($n = 0$ 12), conditioning pulse-trains at low and fast frequencies were successively applied to compare their relative efficiency (Figs. 3 and 5). Rhythmic pulse-trains induced different degrees of facilitation of tested EPSPs in 41 of 42 tested neurons, regardless of the frequency used for the conditioning stimulation. Similar results were obtained in areas 5 and 7.

With conditioning pulse-trains delivered at frequencies of 10 or 20 Hz, the test EPSPs amplitudes increased similarly (~54% in neuron depicted in Fig. 2A, the highest potentiation seen with conditioning pulse-trains at these relatively low frequencies). In a neuronal sample ($n = 17$) tested with pulse-trains at 10–20 Hz as conditioning stimulation, all neurons displayed potentiation of tested EPSPs. The amplitudes of control EPSPs (in mV) were 5.41 ± 0.83 and 6.7 ± 0.94 after conditioning stimulation. The average potentiation was 24%.

With higher frequency (40–50 Hz) as conditioning stimulation (Fig. 2B), all 41 neurons displayed potentiation of tested EPSPs. The amplitude of test EPSPs (in mV) was 6.5 ± 0.7, whereas conditioned EPSPs had amplitudes of 7.9 ± 0.7; the
FIG. 2. Potentiation of callosally evoked EPSPs after rhythmic stimulation at 10 and 50 Hz. Barbiturate anesthesia. A and B: RS and fast-rhythmic-bursting (FRB) neurons. A: top trace depicts spontaneous neuronal activity in area 5 and 4 stimuli (arrowheads) applied every 2 s. Bottom left: superimposed averaged (n = 20 sweeps) control responses (dotted line) and responses after conditioning stimulation at 10 Hz (continuous line). Right: plot of EPSPs amplitudes (dotted lines indicate mean amplitudes in millivolts) before and after pulse-trains at 10 Hz. B: potentiation of callosally evoked EPSPs after rhythmic stimuli at 50 Hz. Similar arrangement as in A with superimposed averaged (n = 20 sweeps). Significance of changes from control to conditioned responses are shown (t-test, **P < 0.01; ***P < 0.001; --, ns)
average percentage of potentiation was 21%. A similar degree of facilitation was seen with conditioning pulse-trains at 100 Hz (data not shown; see Figs. 5B and 6). The time-course of facilitated EPSPs varied among tested neurons. In the FRB neuron depicted in Fig. 2B, the potentiation lasted ~4 min (t-test, \( P < 0.001 \)).

An example of the residual facilitation of tested EPSPs, for periods lasting from 18 to 30 min (\( n = 27 \)), is shown in
Fig. 3, A and B, which also compares the effects exerted by low (10 Hz) and fast (40 Hz) frequencies of conditioning pulse-trains. In this RS neuron, the facilitation induced by 10 Hz stimulation was \( \frac{50\%}{t\text{-test}, P \leq 0.01} \) and lasted for \( 25 \) min, whereas 40-Hz conditioning stimulation further enhanced the amplitudes of EPSPs by \( 24\% \) ( \( t\text{-test}, P \leq 0.05 \)). Figure 3C shows a neuron in which the potentiation lasted for 30 min.

We also examined the potentiation after successive conditioning 50-Hz pulse-trains applied to callosal pathway after complete recovery following the first conditioning pulse-train ( \( n = 7 \) RS neurons). Figure 4, A and B, shows that, after decreasing amplitudes of EPSPs to control level ( \( \sim 9.5 \) mV in A, \( \sim 1.7 \) mV in B), there was again an increased amplitude after the second conditioning pulse-train (although the potentiation was slightly weaker), with highly significant enhancement ( \( P \leq 0.01 \) and \( P \leq 0.001 \)).

**EPSPs potentiation by successive pulse-trains with different frequencies under barbiturate anesthesia**

To determine whether preferred frequencies of conditioning stimulation are detectable, we applied pulse-trains with incremental and decremental frequencies, i.e., from lower to higher and back to lower frequencies, and in decremental way, i.e., from higher to lower frequencies (Fig. 5, A and B).
Data in Fig. 5A show progressively increased facilitation of test EPSPs by increasing the frequency of conditioning stimulation from 10 to 70 Hz and depression from 70 to 10 Hz. If conditioning stimuli started with higher frequencies, facilitation was only induced by the early conditioning pulse-train, and test EPSPs diminished gradually with decreasing frequencies of conditioning stimuli (Fig. 5B). Applying conditioning stimuli with decremental (500–10 Hz) and progressively incremental (10–500 Hz) frequencies (Fig. 5C) showed that 1) when rhythmic pulse-trains were applied in decremental way, single test EPSPs depressed gradually from higher to lower frequencies (300–10 Hz); whereas 2) when rhythmic pulse-trains were applied in incremental way, single test EPSPs increased gradually after each rhythmic pulse-trains from 10 to 100 Hz and thereafter remained virtually constant from 120 to 500 Hz.

Comparison between potentiation in neurons recorded in stimulated and naïve pathways

We analyzed changes in amplitude of EPSPs in a population of neurons in which successive control-conditioned EPSPs
were recorded in the same experiment ($n = 42$) compared with changes in a subpopulation of neurons ($n = 15$) recorded at the very beginning of each experiment, in which the stimulation protocol was applied for the first time (Fig. 6). Figure 6B shows similar enhancement in those neurons that were potentiated by stimulating a naïve callosal pathway. In these experiments, a smaller number of neurons displayed small (<10%) amplitude changes, suggesting that potentiation of the stimulated pathways lasted for very long periods of time and that, once potentiated, the pathway could only slightly be further potentiated.
FIG. 7. Potentiation of callosally evoked EPSPs is dependent on N-methyl-D-aspartate (NMDA) receptors. Barbiturate anesthesia. A and B: 2 RS neurons. A: left: EPSP amplitudes before and after pulse-trains at 40 Hz during the control condition (without AP-5). Top: averaged EPSPs (n = 20 sweeps) evoked by stimulating the homotopic site in the contralateral area 5. Right: same arrangement during AP-5 microdialysis. B: left: another neuron recorded shortly within the same track, during the continuing AP-5 microdialysis. Right: after washing. C: callosally evoked EPSPs were measured after rhythmic pulse-trains at 40–50 Hz and compared with control EPSPs for each neuron (n = 7) to evaluate the facilitation in percentage during control and during AP-5 microdialysis. Statistical tests are shown (t-test, **P < 0.01; —, ns).
Reduction in EPSPs potentiation during AP-5 microdialysis in barbiturate-anesthetized animals and under ketamine-xylazine anesthesia

To test the possible participation of NMDA receptors in the callosally evoked potentiation of EPSPs, seven neurons were recorded under barbiturate anesthesia before and after AP-5 microdialysis. The amplitudes of control EPSPs diminished by ~20% during AP-5 microdialysis, and the facilitation induced by conditioning 40-Hz pulse-trains was also reduced from 40% (t-test, P < 0.01), before microdialysis, to 8% (t-test, P > 0.4), during microdialysis (Fig. 7A). In another RS neuron, conditioning pulse-trains at 40 Hz were first delivered during the application of AP-5 and then after washing. Similarly, the amplitude of control EPSPs was lower under AP-5 than after washing: the conditioning protocol induced no significant change under AP-5 (t-test, P > 0.1) and a potentiation of 56% (t-test, P < 0.01) after washing (Fig. 7B). The plot in Fig. 7C, with the results from seven neurons, shows that AP-5 microdialysis strikingly reduced or abolished the EPSPs’ potentiation by pulse-trains at 40–50 Hz.

In keeping with the above results of AP-5 microdialysis, none of the 10 neurons recorded under ketamine-xylazine anesthesia displayed potentiation of callosally evoked EPSPs following all frequencies used for conditioning stimulation, from 10 to 100 Hz (Fig. 8). It is known that ketamine is a powerful blocker of the NMDA subtype of excitatory amino acid receptor (MacDonald et al. 1991).

DISCUSSION

The major findings in our study are as follows. 1) Conditioning stimulation of callosoal pathway induces homosynaptic facilitation (~20–25%) of callosally evoked EPSPs in animals under barbiturate anesthesia, which does not necessarily require high-frequency stimulation since the potentiation is present at all frequencies from 10 to ~200 Hz. 2) The EPSPs potentiation lasted from 2–4 min to ~20–30 min. 3) The EPSPs’ potentiation was reduced during AP-5 microdialysis in barbiturate-anesthetized animals and was not present under ketamine-xylazine anesthesia.

In the hippocampus, synaptic potentiation was induced in a number of ways, generally by delivering a train of 50–100 stimuli at 100 Hz or higher frequency (Bliss and Collingridge 1993; Bliss and Lømo 1973; Rose and Dunwiddie 1986). The “theta-burst stimulation” is one of the favored protocols to study synaptic facilitation; however, the frequency of stimulation must be ≥100 Hz, and it may fail to induce synaptic facilitation when interstimuli intervals between theta-bursts are <1 s (Larson et al. 1986).

Compared with the above studies, the protocol used in this study shows that, in the callosal pathway, the interstimuli intervals between pulse-trains may be 2–3 s and that stimulation with relatively low frequencies (10–20 Hz) can also induce EPSPs’ facilitation. Earlier studies have reported that stimulation with frequencies between 5 and 15 Hz, mainly 10 Hz, produces augmenting responses in thalamocortical systems in vivo (Ferster and Lindström 1985; Morin and Steriade 1981; Morison and Dempsey 1942; Steriade et al. 1998b), in vitro (Castro-Alamancos and Connors 1996), and in computo (Bazhenov et al. 1998). In vivo studies have shown that augmentation of responses during pulse-trains at 10 Hz and outlasting the stimulation period is also induced in the thalamus of decorticated animals (Steriade and Timofeev 1997; Timofeev and Steriade 1998), in neocortical areas after lesions of the appropriate thalamic nuclei (Morin and Steriade 1981; Steriade and Yossif 1974), and in disconnected neocortical slabs (Timofeev et al. 2002). Thus both the thalamus and neocortex have the required neuronal machinery to elaborate synaptic plasticity. However, although the augmented cortical response to 10 Hz stimulation follows the first action potential of the rebound spike-burst in the simultaneously recorded thalamocortical neuron by ~3 ms (Steriade et al. 1998b), cortical networks have the ability to maintain and develop this form of synaptic plasticity in the absence of the thalamus (Steriade et al. 1993). In the preceding studies on thalamocortical and intracortical systems, we used limited low-frequency stimulations (around 10 Hz), simulating sleep spindles. Below 5 Hz, augmented thalamocortical potentials could not be generated because successive stimuli reached the cortical neuronal pool after the postinhibitory rebound of the preceding response and elicited a primary

![Fig. 8](image-url)
response (see Fig. 4 in Morin and Steriade 1981). Intracellular recordings of thalamic relay neurons in decorticated animals (Steriade and Timofeev 1997) similarly showed that responses did not significantly change with successive stimuli <5 Hz.

One of the major findings in this study is that the callosal pathway displays potentiation of single EPSPs at all conditioning frequencies between 10 and ~200 Hz, in virtually all tested neurons (41 of 42). This homosynaptic potentiation stands in contrast with the depression in neocortical neurons when using cortical and thalamic paired stimuli at intervals <50 ms, corresponding to frequencies >20 Hz (Fuentebalba et al. 2004). The presence of potentiation in the callosal pathway with conditioning pulse-trains at high frequencies (~50–200 Hz) may be ascribed, at least partially, to the co-existence of NMDA receptors at callosal synapses (Kumar and Huguenard 2001) and the fact that high-frequency stimulation, typically ≥100 Hz, activates the NMDA channel to generate a large Ca2+ influx and induce prolonged potentiation (Artola and Singer 1990; Herron et al. 1986). Indeed, our experiments showed that microdialysis with NMDA receptor blocker AP-5 significantly reduced the callosal potentiation of tested EPSPs.

By applying rhythmic pulse-trains to contralateral cortical areas, we induced facilitation of tested EPSPs, which could last for about 20–30 min. It is conceivable that various (biochemical and/or neuronal) factors acting on cortical neurons during low- or fast-frequency brain rhythms, which were simulated in these experiments, would further amplify their impact on local and distant network to generate paroxysmal discharges. This is especially the case of bursting neurons with high propensity to seizures, such as FRB and IB cells (Grenier et al. 2003; Steriade et al. 1993), since some FRB neurons project to the thalamus (Steriade et al. 1998a) and may further spread the paroxysmal process. Although synaptic plasticity is believed to characterize the cellular mechanism for memory formation (Collingridge et al. 1995), another facet of this phenomenon may be the development from normal to paroxysmal activity.

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