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Short-term synaptic enhancement and long-term potentiation in neocortex

(*N*-methyl-D-aspartate receptors/sensorimotor cortex/facilitation/depression)

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ABSTRACT **Repetitive stimuli reliably induce long-term potentiation (LTP) of synapses in the upper layers of the granular somatosensory cortex but not the agranular motor cortex of rats. Herein we examine, in these same cortical areas, short-term changes in synaptic strength that occur during the LTP induction period. θ-Burst stimulation produced a strong short-term enhancement of synapses in the granular area but only weak enhancement in the agranular area. The magnitude of enhancement during stimulation was strongly correlated with the magnitude of LTP subsequently expressed. Short-term enhancement was abolished by an antagonist of *N*-methyl-D-aspartate (NMDA) receptors but remained in the presence of a non-NMDA receptor antagonist. Inhibitory postsynaptic potentials of the granular and agranular areas displayed similar frequency sensitivity, but the frequency sensitivity of NMDA receptor-dependent excitatory postsynaptic potentials differed significantly between areas. We propose that pathway-specific differences in short-term enhancement are due to variations in the frequency dependence of NMDA currents; different capacities for short-term enhancement may explain why repetitive stimulation more readily induces LTP in the somatosensory cortex than in the motor cortex.**

Brief activity in a synapse often enhances its subsequent strength. The duration of enhancement varies with the type of synapse and the amount and pattern of activation. Several short-term forms of enhancement, including facilitation, augmentation, and potentiation, last from milliseconds to tens of seconds (1). Long-term forms of enhancement include short-term potentiation, which lasts 5–20 min, and long-term potentiation (LTP), which lasts from hours to days (2, 3). Although a single synapse may display several varieties of synaptic enhancement (e.g., ref. 4), few studies have explored the possibility that there are interactions between the short- and long-term forms.

There are reasons to expect that short-term plasticity in a neural circuit might strongly influence the probability of longer-lasting changes, such as LTP, in response to repetitive afferent activity. In some pathways of the cerebral cortex, the induction of LTP depends on an increase of postsynaptic $[Ca^{2+}]$, usually caused by influx of Ca^{2+} through *N*-methyl-D-aspartate (NMDA) receptor channels (3). Postsynaptic $[Ca^{2+}]$ must rise above a certain threshold for LTP to be induced, and strong synaptic strength during the induction phase is more likely to achieve threshold $[Ca^{2+}]$ levels than weak synaptic strength (5). Thus short-term processes that enhance synaptic strength during conditioning stimuli should promote the subsequent expression of LTP.

The propensity to generate LTP varies among synapses of the cerebral cortex (6, 7). Some excitatory pathways of the hippocampus produce robust forms of NMDA-receptor-dependent LTP; in contrast, NMDA-receptor-dependent LTP in the neocortex tends to be smaller in amplitude and more difficult to elicit, although several stimulus protocols applied to the primary visual cortex can be effective (e.g., refs. 8–10). We have found (11) that two cytoarchitectonic areas of neocortex, stimulated under similar conditions, differed greatly in their ability to generate LTP. θ-Burst stimulation (TBS) applied to layer IV of the granular primary somatosensory area reliably induced LTP in layer II/III, while the same procedure applied in the agranular primary motor area did not induce lasting changes. The aim of the present study was to identify mechanisms in the pathways of granular and agranular neocortex that might explain their distinctly different capacities to generate TBS-induced LTP. The results show that there are pathway-specific differences in the short-term regulation of NMDA-receptor-dependent events that may underlie the differences in long-term NMDA-receptor-dependent potentiation.

MATERIALS AND METHODS

The methods used in this study were similar to those as described (11). Sprague–Dawley rats (>150 g; >40 days old) were used. Slices from frontoparietal neocortex were bathed in control buffer containing 124 mM NaCl, 5 mM KCl, 1.25 mM NaH_2PO_4, 2 mM $MgSO_4$, 2 mM $CaCl_2$, 26 mM $NaHCO_3$, and 10 mM dextrose, at 35.5°C.

When drugs were used, they were either dissolved in the recording pipette solution or in the bathing solution. The concentration of bicuculline methiodide (BMI) was 50 μM in the bathing buffer. D-2-Amino-5-phosphonovaleric acid (AP5) was applied as 10 mM in 0.25 M NaCl in the pipette or 100 μM in the buffer. Nifedepine was dissolved in dimethyl sulfoxide at 1 M and then diluted to a final concentration of 10 mM in 0.25 M NaCl in the pipette. The antagonist 6,7-dintroquinoxaline-2,3-dione (DNQX) was added as 20 μM or 80 μM in the bathing solution. Drugs were purchased from Sigma or Research Biochemicals International.

RESULTS

Short-Term Enhancement Is Prominent in Granular, but not Agranular, Cortex. Synaptic responses changed dramatically during TBS, and the changes were area-specific. Fig. 1*A* shows intracellular recordings during the first, third, and sixth sequences of TBS. In neurons of the granular cortex, but not the agranular cortex, the response to each burst was generally enhanced. Responses to the very first burst were similar in the

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Abbreviations: TBS, θ-burst stimulation; LTP, long-term potentiation; AP5, D-2-amino-5-phosphonovaleric acid; NMDA, *N*-methyl-D-aspartate; IPSP, inhibitory postsynaptic potential; GABA, γ-aminobutyric acid; EPSP, excitatory postsynaptic potential; DNQX, 6,7-dintroquinoxaline-2,3-dione; BMI, bicuculline methiodide.

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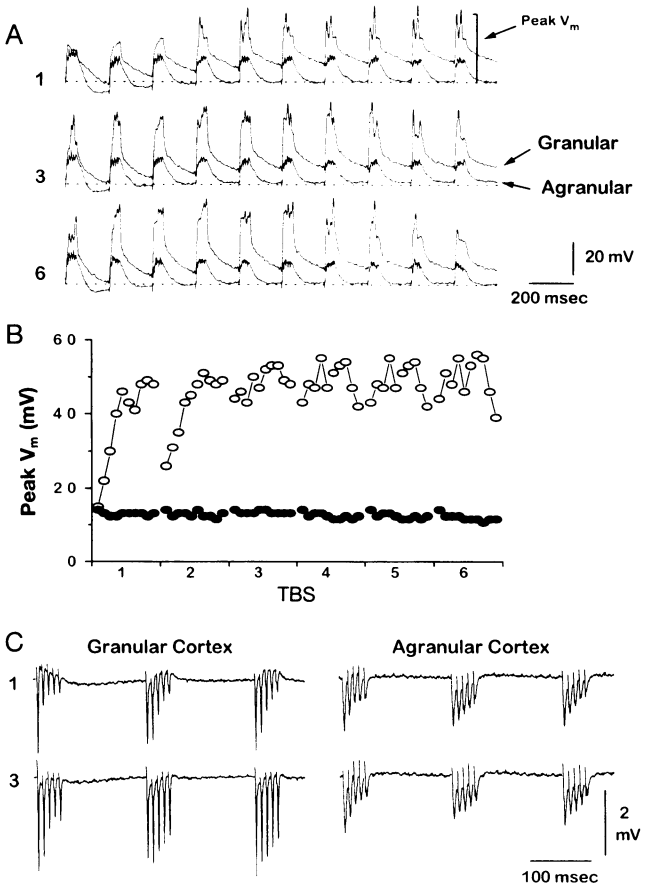

FIG. 1. Short-term response changes during TBS in the granular and agranular areas. (*A*) Short-term enhancement in granular cortex, but not agranular cortex. Superimposed intracellular recordings from two neurons, one in each area, in response to the entire first, third, and sixth TBSs. Burst responses from the granular cortex progressively increased during each sequence and from one sequence to the next; responses from the agranular cortex changed little during the entire six sequences. Traces have been filtered to reduce action potential contributions. (*B*) Change in peak membrane potential (V_m; measured as shown in upper trace of *A*) during TBS in neurons from the granular (open circles; $n = 3$) and agranular (solid circles; $n = 3$) cortex. (*C*) Extracellular field potential recordings during TBS in the granular and agranular areas, showing the three first bursts of the first and third TBS in each area. Note that responses of the granular cortex, but not agranular cortex, showed enhancement within bursts and within and across sequences. TBS consisted of six sequences of shocks spaced 10 sec apart. Each sequence consisted of 10 bursts (five shocks at 100 Hz) delivered at 5 Hz.

two cells, but all subsequent responses were much larger in the granular cortical neuron. Graphical display of the mean results from three granular neurons shows that they substantially increased their peak levels of depolarization (Fig. 1*B*, open circles) during each early TBS sequence and across the first several sequences. Neurons in agranular cortex showed no increases in peak responses either within or between sequences (Fig. 1*B*, solid circles). Fig. 1*C* shows extracellular recordings of the first few burst responses of sequences 1 and 3 from granular and agranular cortex. In both cortical areas, the five responses during the first burst were progressively depressed. This intraburst depression was consistent from burst-to-burst in agranular cortex. However in granular cortex, intraburst depression was largely abolished during TBS. We will refer to these general TBS-related increases of synaptic response (whether intraburst, interburst, and intersequence) as "short-term enhancement."

Correlation Between Short-Term Enhancement and LTP. In a previous study (11), we found that TBS could induce LTP in the granular area but not in the agranular area. Fig. 2*A* illustrates examples of the differential long-term effects of TBS applied in each area, by using extracellular field potentials recorded before and after TBS. Both response amplitudes and slopes were elevated in the granular area but not in the agranular area.

We estimated the magnitude of short-term enhancement from the percentage change of the mean response to the fifth TBS relative to that of the first TBS. The magnitude of LTP was defined as the percentage of change 30 min after TBS, relative to the pre-TBS baseline. Fig. 2*B* plots data from 36 drug-free slices from granular and agranular cortex. There is a strong and significant correlation between short-term enhancement and LTP overall ($r = 0.9$; $P < 0.0001$). The clustering of open and solid points on the graph (Fig. 2*B*) also illustrates the differences between granular and agranular areas in their expression of both enhancement and LTP.

We tested whether the induction of short-term enhancement *per se* is sufficient for inducing LTP. One TBS applied to granular cortex consistently caused enhancement (see Fig. 1 *A* and *B*), but it was not enough to induce LTP; instead, short-term potentiation lasting <20 min was induced (see ref. 12). LTP required three or more TBSs ($n = 5$; data not shown).

Dependence of Short-Term Enhancement on NMDA-Receptor Activation. The circles in Fig. 3*A* plot data from field potential measurements taken in control granular and agranular cortical slices (the mean of 10 slices of each area). Extra-

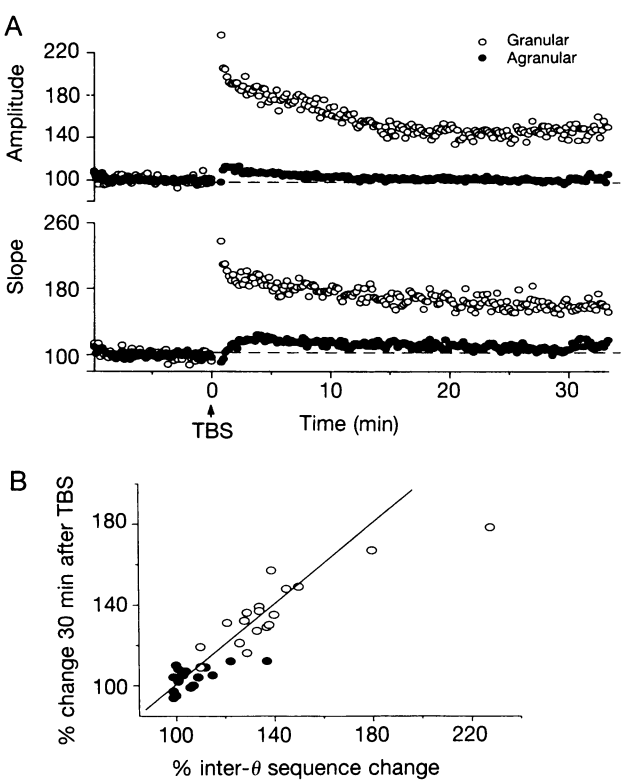

FIG. 2. Long-term consequences of TBS in the granular and agranular areas. (*A*) Graphs of the slope and amplitude of field potentials before and after TBS, calculated as a percentage of the mean pre-TBS response. LTP was induced in the granular, but not in the agranular, region. (*B*) Correlation between the magnitudes of short-term enhancement and LTP for granular (open circles) and agranular (solid circles) cortex. The amplitude of short-term enhancement was defined as the percentage change in the mean response to the fifth TBS relative to that of the first sequence (percent inter-θ sequence change). The magnitude of LTP was defined as the percentage of slope change 30 min after TBS, relative to pre-TBS baseline. A significant positive correlation was observed ($r = 0.9$; $P < 0.0001$). The straight line has a slope of 1.0 for comparison.

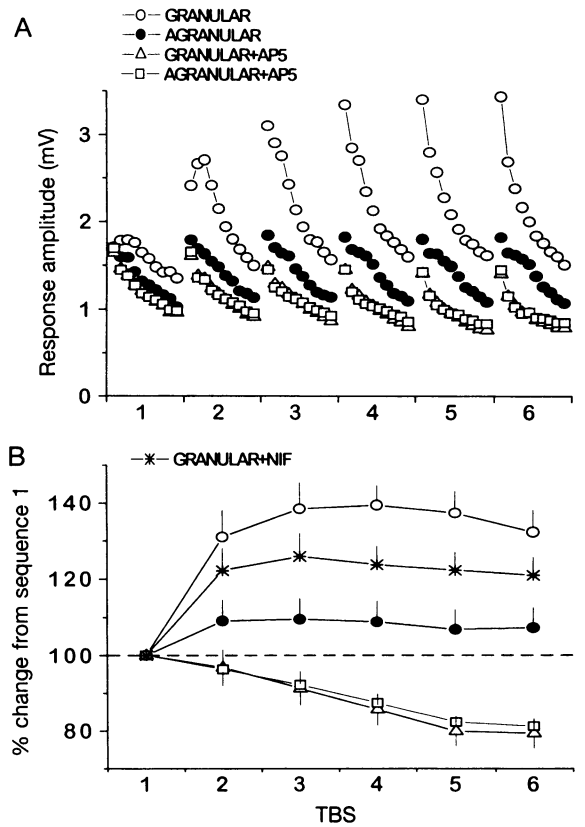

FIG. 3. AP5 blocks short-term enhancement. (*A*) TBS-induced field potentials recorded under control conditions showed strong enhancement in the granular area and slight enhancement in the agranular area. In the presence of AP5, enhancement was abolished in both areas. Each point represents the average amplitude of the five pulses and responses during each burst (as in Fig. 1*C*); they are grouped by sequence, 10 bursts per sequence. (*B*) Summary of responses during TBS under different experimental conditions, recorded as in *A*. Each point is the mean ± SEM of all response amplitudes within that sequence, normalized to the mean of the first sequence (8–12 experiments per data set). In the presence of AP5, enhancement was absent in both cortical areas. In addition, the effect of nifedipine in the granular cortex is also illustrated.

cellular burst responses declined within each TBS in both areas, but during the first sequence they fell most rapidly in agranular cortex. During subsequent sequences, there was a general enhancement of responses in granular cortex, while enhancement in agranular cortex was minimal. The data are summarized in Fig. 3*B*, which plots the normalized mean responses for each TBS; responses plateaued at less than 109% in agranular cortex (solid circles) and at about 140% in granular cortex (open circles). In both cortical areas, the application of the NMDA antagonist AP5 abolished enhancement without reducing the initial burst response (Fig. 3*A*; n = 8). In the presence of AP5, TBS caused a small and progressive intersequence depression that was identical in the two cortical areas (Fig. 3, triangles and squares).

We previously showed that nifedepine, an L-type calcium channel blocker, only slightly depressed the production of LTP in granular cortex (11). Nifedepine also somewhat diminished TBS-induced short-term enhancement in granular cortex (Fig. 3*B*, crosses; n = 12 slices) compared to control cortex. Nevertheless, short-term enhancement in the nifedepine-treated granular area was still significantly larger than enhancement in the control agranular cortex.

TBS-Induced Disinhibition Is Similar in Granular and Agranular Cortex. Inhibitory postsynaptic potentials (IPSPs) are usually depressed by repetitive activation (13, 14). We reasoned that short-term enhancement might be stronger in granular cortex because its IPSPs are depressed more during TBS than those in the agranular cortex. Neurons were recorded intracellularly in the presence of DNQX (20–80 μM) and AP5 (100 μM) to block non-NMDA and NMDA receptors. IPSPs were evoked by TBS stimulation nearby, while membrane potential was adjusted to be close to −55 mV. The amplitude of each burst-induced IPSP was measured and used as an estimate of synaptic strength (Fig. 4*A*). IPSPs in both cortical areas were progressively and similarly depressed during each TBS sequence (n = 6 neurons from each area; quantification not shown). Neither cortical area showed much change in mean IPSP size across sequences (Fig. 4*B*). The data imply that a difference in stimulus-induced disinhibition cannot be the basis for the stronger short-term enhancement displayed by granular cortex, as compared to agranular cortex.

Enhancement of NMDA-Receptor-Mediated Excitatory Postsynaptic Potentials (EPSPs) in Granular, but not Agranular, Cortex. EPSPs in the neocortex have both NMDA- and non-NMDA-receptor-dependent components (15–17). Since non-NMDA-receptor-dependent excitation did not show enhancement (AP5-treated slices in Fig. 3), and IPSPs did not decline across TBSs (Fig. 4), we tested whether NMDA-receptor-dependent responses showed enhancement. In the presence of DNQX (20 μM) to block non-NMDA receptors and 1 mM Mg^{2+}, relatively slow AP5-sensitive responses were recorded both extracellularly and intracellularly (Fig. 5*A*). Under these conditions, TBS in the granular cortex caused a strong enhancement (Fig. 5*B*; n = 6 slices; open circles). In contrast, in agranular cortex enhancement was negligible (Fig. 5*B*; n = 6 slices; solid circles).

Although the previous experiment showed that NMDA-receptor-mediated postsynaptic potentials responded differently to TBS in the two cortical areas, the difference could still be attributed to some feature of the inhibitory circuits, which were not blocked. For instance, changes could occur at the excitatory synapse with the inhibitory interneuron. Thus, we tested the behavior of NMDA-receptor-mediated EPSPs in the

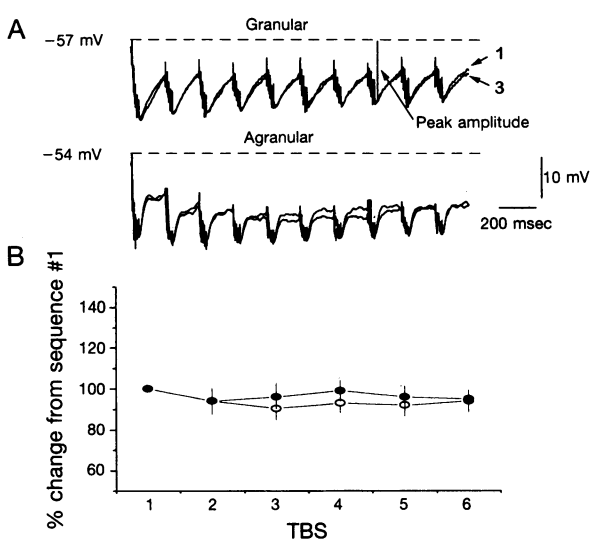

FIG. 4. Effects of TBS on IPSPs in the granular and agranular cortex. (*A*) Examples of intracellular recordings from cells in the granular cortex (upper traces) and agranular cortex (lower traces) showing responses to the first and third TBSs. Recordings were made in the presence of AP5 (100 μM) and DNQX (20 μM), and cells were depolarized with injected current of about 0.3 nA to the membrane potentials shown at left. The difference in decay time course between the illustrated cells was not a consistent finding. (*B*) Stability of IPSPs across TBSs in both cortical areas. Data points are the mean response amplitude (±SEM) of six cells per group, normalized to the first sequence response.

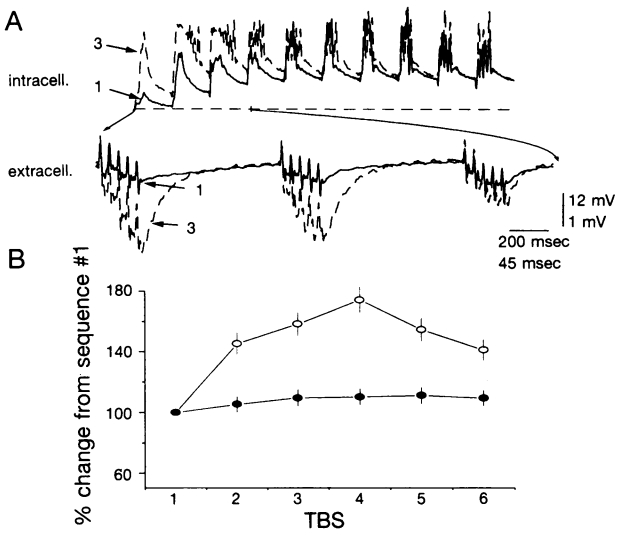

FIG. 5. Enhancement of NMDA-receptor-dependent EPSPs in the granular, but not the agranular, cortex in the presence of inhibition. (*A*) NMDA-dependent events measured intracellularly (upper traces) and extracellularly (lower traces) in granular cortex, in the presence of 1 mM Mg^{2+} and 20 μM DNQX. Responses showed inter-θ sequence enhancement (compare response to the first and to the third θ sequence). The extracellular recording shows only the response to the three first bursts of sequences 1 and 3 for clarity. (*B*) Short-term enhancement of the NMDA-dependent responses in the granular (open circles) and agranular (solid circles) areas during TBS. Each point is the mean ± SEM of the extracellular response amplitude within a sequence, normalized to the first sequence response. Data are the mean of six experiments per group.

presence of BMI (50 μM) to block type A γ-aminobutyric acid ($GABA_A$) receptor-mediated inhibition and DNQX (20 μM) to block non-NMDA receptors. The usual epileptiform consequences of disinhibition (18) were minimized by surgically removing the deep cortical layers. NMDA EPSPs were measured while depolarizing all neurons to between −55 and −60 mV. During TBS, NMDA-receptor-mediated EPSPs were depressed from burst to burst within a sequence (Fig. 6*A*; each trace is the average response of 10 neurons from each area). However, the magnitude of depression was much smaller in neurons from granular cortex than in those of agranular cortex (Fig. 6*B*; means of 10 neurons from each area). While the amplitude of the response to the first burst did not differ between cortical areas, the amplitudes of all subsequent EPSPs (bursts 2–10) were significantly larger in the granular cortex neurons ($P < 0.0001$; two-tailed t test). Depression of EPSPs in agranular neurons was accompanied by a slow membrane hyperpolarization that peaked after the first θ burst and decayed back to baseline during the 10-burst sequence (Fig. 6*A*). Nevertheless, the NMDA EPSPs remained small throughout the burst sequence, implying that the small slow hyperpolarization alone cannot account for the relatively much greater depression in agranular neurons. It is important to note that the addition of BMI eliminated the usual depolarizing shift of baseline membrane potential observed during TBS application (Fig. 1*A*). This shift was similar in both cortical areas in the presence of AP5 and was due to the frequency-dependent depression of IPSPs (data not shown).

During the course of these experiments in DNQX and BMI, we fortuitously recorded one granular area neuron with the fast-spiking characteristics that are diagnostic of certain GABAergic interneurons (19, 20). Subsequently, just adjacent to the fast-spiking cell, we recorded a neuron with the regular-spiking characteristics of pyramidal cells. As shown in Fig. 6*C*, responses of both cells were depressed during TBS sequences.

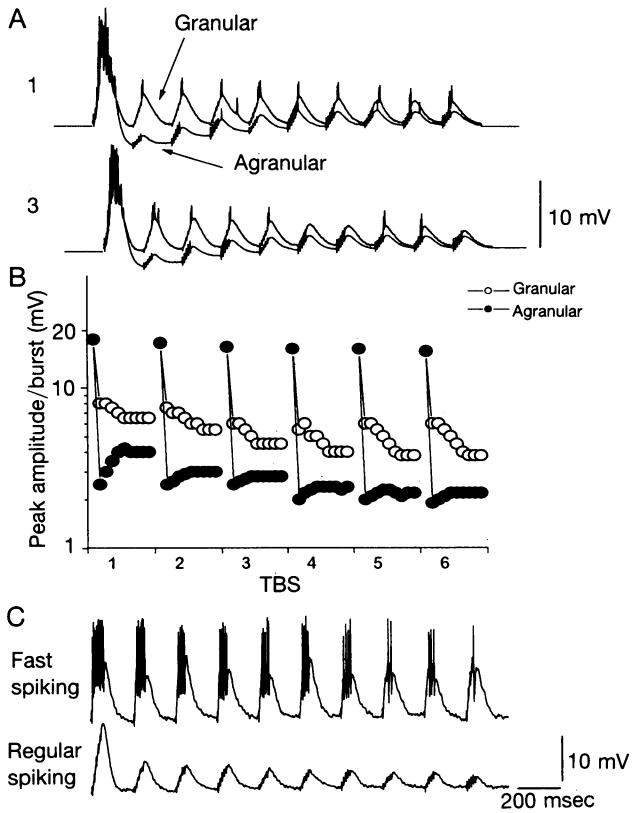

FIG. 6. Differential regulation of isolated NMDA EPSPs in granular and agranular cortex. (*A*) Average intracellular response (10 neurons from granular and 10 neurons from agranular cortex) in the presence of 50 μM BMI and 20 μM DNQX to the first and third TBSs. Note the stronger depression of responses in the agranular neurons. (*B*) Mean peak amplitude to each burst response from a TBS in the granular and agranular areas. Data were taken from the cells illustrated in *A* (10 neurons per group). For clarity, SEMs are not plotted, but they represented less than 5% of the means. (*C*) Sequentially recorded intracellular responses of a fast-spiking cell and a regular-spiking cell in the same electrode penetration from a slice of granular cortex. Each trace shows a response to a TBS sequence, using the same stimulation intensity and under the same pharmacological conditions described above (i.e., BMI and DNQX). Note that in both cell types the NMDA EPSPs were depressed from the second through subsequent bursts. Recordings have been filtered to reduce spike amplitude.

This similarity suggests that presynaptic mechanisms may contribute to interburst depression.

DISCUSSION

The most important findings in this study were (*i*) synaptic responses in the granular area, but not in the agranular area, were strongly enhanced during repetitive θ-burst patterns of stimulation, (*ii*) this short-term enhancement was dependent upon NMDA receptors, but not non-NMDA receptors, (*iii*) the frequency sensitivity of inhibition was similar in the two cortical areas, (*iv*) isolated NMDA-receptor-dependent EPSPs were more resistant to repetitive activation in the granular area than in the agranular area, and (*v*) the magnitude of short-term enhancement during TBS was strongly correlated with the magnitude of LTP subsequently expressed.

We found that the short-term enhancement evident in granular cortex depends in large part on NMDA-receptor-mediated components of the EPSPs. It follows that short-term enhancement will lead to strong NMDA currents with a large Ca^{2+} influx, high postsynaptic [Ca^{2+}], and an enhanced probability of LTP expression. If short-term enhancement is weak or absent, as in agranular cortex, NMDA currents and postsyn-

aptic [Ca^{2+}] increases will be minimized during repetitive activation. It could still be suggested that enhancement is just the early expression of LTP. However, since one TBS triggers enhancement but not LTP, enhancement and LTP must be separate processes.

Why does the activated pathway in granular cortex exhibit short-term enhancement during TBS, while the analogous pathway in agranular cortex does not? (*i*) It is likely that the mixture of axons activated in each area is different. In layer IV of the granular cortex, there are densely packed spiny stellate cells whose axons project strongly to layer II/III. These axons are absent in agranular cortex. Different types of cortical axons may have different functional and molecular properties (21). (*ii*) Our results implicated NMDA receptors in the difference between areas. Synaptic inhibition was depressed during repetitive stimulation, but with a similar time course and magnitude in the two areas. Elimination of non-NMDA receptor contributions did not suppress enhancement or its area specificity (Fig. 5), so we can conclude that non-NMDA receptor activation is not necessary for enhancement. In contrast, the frequency-dependent depression of isolated NMDA EPSPs was much stronger in agranular than in granular neurons, suggesting a differential regulation of NMDA-receptor-mediated currents. During a TBS sequence, the interplay between progressive depression of inhibition and NMDA-receptor-mediated excitation (cf. ref. 22) will, on balance, yield a larger response in neurons of granular cortex, because their NMDA currents are less prone to depression than those in agranular neurons.

There are numerous mechanisms by which NMDA-receptor-mediated currents might be differentially regulated. It is possible that different NMDA receptor subtypes are expressed in each cortical area (23), and so there might be channel-specific differences in kinetics, desensitization (24, 25), or second messenger-mediated modulation (26). There may also be variations in the density of presynaptic receptors for modulators that control transmitter release, such as GABA or adenosine (27). A likely modulator is GABA acting through $GABA_B$ receptors located either presynaptically (28) or postsynaptically (29). One scenario would be that axons from layer IV spiny stellate cells, which are present in the granular cortex but not in agranular cortex, are relatively insensitive to modulators that act upon presynaptic receptors to diminish transmitter release. The selective presence of these presynaptic fibers in granular but not agranular cortex could explain why agranular cortex is less capable of generating enhancement and subsequently LTP in response to θ-burst stimulation. Similarly, this could explain why LTP induction in visual cortex is more reliably generated by activation of layer IV than by afferents from the white matter (6).

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