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Long-term potentiation is associated with increased [^{3}H]AMPA binding in rat hippocampus

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The location and nature of the changes underlying long-term potentiation (LTP) remain controversial issues. In this study, we tested the possibility that changes in binding properties of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA)/quisqualate and *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors are associated with LTP. LTP was elicited in vivo by stimulation of the perforant pathway in anesthetized rats. One hour following stimulation the animals were sacrificed. We performed quantitative ligand binding autoradiography on frozen brain sections using [^{3}H]AMPA and [^{3}H]*N*-(1-(2-thienyl)cyclohexyl)-3,4-piperidine ([^{3}H]TCP) to label the AMPA/quisqualate and the NMDA receptors, respectively. No changes in [^{3}H]TCP binding were detected in any of the treatment groups. However, increases in [^{3}H]AMPA binding were observed only in animals that exhibited LTP. These increases were bilateral and present in several subfields of the hippocampus and cortical areas. Administration of the NMDA receptor antagonist, ketamine, prior to tetanic stimulation prevented both the increase in binding and the induction of LTP. These results suggest that changes in the characteristics of AMPA/quisqualate receptors are a biochemical correlate of LTP.

INTRODUCTION

Long-term potentiation (LTP) is defined as a long-lasting enhancement of synaptic efficacy occurring at excitatory synapses in the mammalian brain following brief trains of high-frequency electrical activity applied to afferent pathways[4]. LTP has been reported to occur in the cerebral cortex[16,18,32], superior colliculus[25] and amygdala[6,7], but is most prominent and has been most extensively studied in the hippocampal formation[17,19,32,39]. Several properties of LTP such as its rapid induction, relatively long half-life and synaptic specificity have led to the suggestion that it is involved in the formation and storage of memories[37,38].

The induction of LTP in the CA1 region of the hippocampus and the dentate gyrus requires the activation of postsynaptic *N*-methyl-D-aspartate (NMDA) receptors (a subclass of glutamate receptors) and a consequent rise in intracellular calcium concentration[8,21,23,27]. Competitive and non-competitive antagonists of the NMDA receptor prevent the formation of LTP and have been found to impair the acquisition of several hippocampally dependent learning tasks[27,28,33,36].

Recent studies have suggested that the increase in synaptic efficacy associated with hippocampal LTP results from a postsynaptic change in some properties of postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors (a subclass of glutamate receptors)[12,15,29,30,35]. Specifically, Muller et al.[29] reported that LTP in the CA1 region of hippocampal slices was associated with a larger increase in the fast, 6,7-dinitro-quinoxaline-2,3-dione (DNQX)-sensitive (quisqualate receptor-mediated) component of the evoked field potential, than in the slower, D-2-amino-5-phosphonopentanoate (D-AP5)-sensitive (NMDA receptor-mediated) component. Similarly, aniracetam, a compound that selectively increases the conductance of AMPA receptors[14], has proportionately smaller effects on potentiated synapses than non-potentiated synapses[35]. Although there have been reports of an increase in presynaptic glutamate release following LTP induction[5,22], others have failed to observe such a change[1,12].

Further support for a role of postsynaptic AMPA receptors in the expression of potentiated synaptic transmission comes from studies of nictitating membrane (NM) conditioning in rabbits. During NM conditioning the hippocampus exhibits massive training-induced neuronal plasticity that is highly correlated with the production of conditioned NM extensions[2,3]. Furthermore, the acquisition of the conditioned response is paralleled by

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LTP-like increases in perforant path-evoked dentate field potentials[43]. Recently, Tocco et al.[40] reported that this type of learning is associated with an increase in the affinity of AMPA receptor agonists. These studies suggest that the hippocampal plasticity observed during NM conditioning involves LTP expression mechanisms through a modification of postsynaptic AMPA receptors.

To further examine the role of postsynaptic glutamate receptors in LTP, we performed ligand-binding autoradiography on brain sections from rats which received high-frequency theta burst stimulation (TBS) to the perforant pathway under anesthesia. The binding was performed with [^{3}H]AMPA and [^{3}H]*N*-(1-(2-thienyl)cyclohexyl)-3, 4-piperidine ([^{3}H]TCP), two ligands specific for AMPA and NMDA receptors, respectively.

MATERIALS AND METHODS

Subjects and surgery

Twenty-six male Long–Evans rats (250–300 g; Simonsen Labs) were pair housed and maintained on ad libitum water and rat chow on a 12-h light/dark cycle.

Prior to electrophysiological testing, rats were anesthetized with an intraperitoneal (i.p.) injection (60 mg/kg of sodium pentobarbital, 65 mg/ml) and mounted in a Kopf stereotaxic frame; the head position was adjusted to place bregma and lambda in the same horizontal plane. After retraction of the scalp, burr holes of approximately 2 mm diameter were drilled unilaterally in the skull (left hemisphere) for the placement of stimulating and recording electrodes. The recording electrode was implanted in the hilus of the dentate gyrus (3.3 mm posterior, 2.4 mm lateral, and 2.8–3.0 mm ventral to bregma) and the bipolar stimulating electrode in the medial perforant pathway (8.1 mm posterior, 4.4 mm lateral, and 2.5–4.0 mm ventral to bregma). The electrodes consisted of Epoxylite-coated stainless-steel pins with the recording and stimulating surfaces formed by removing the insulation at the tips (tip lengths = 50 and 500 μm for the recording and stimulating electrodes, resp.). The ventral locations of both the recording and stimulating electrodes were adjusted to maximize the amplitude of the perforant path-evoked hilar responses. Body temperature was kept at approximately 37°C with a heating pad; the subjects were not artificially respirated. Surgical anesthesia was maintained with hourly injections (0.2 ml) of pentobarbital.

Electrophysiology

Electrophysiological testing (100 μs pulses at 0.05 Hz; voltage adjusted to elicit an approximately 1 mV population spike (PS)) began after stable dentate hilar field potentials had been maintained for at least 30 min. Perforant path-evoked hilar responses were amplified (gain = 100), band-pass filtered (1–2000 Hz), digitized and sampled at 10 kHz using an AST Premium 386c computer (data acquisition software from BrainWave Systems, Boulder, CO).

Evoked dentate hilar responses were recorded during a 20 min interval before and a 30 min interval following high- or low-frequency stimulation of the perforant path. Six subjects (Theta group) received high-frequency TBS (ten 40 ms 400 Hz bursts delivered at 5 Hz, voltage sufficient to elicit a 1 mV PS), 5 subjects (Theta* group) received high intensity TBS (tetanus delivered at a voltage twice that which elicited a maximal PS), and 5 subjects (LF group) received low-frequency stimulation (1 Hz for 200 s). Five additional animals (Sham group) received electrode implantation without electrical stimulation. Input/output (I/O) functions consisting of 3 averaged field potentials at each of 5 different stimulation intensities (range, 1–10 V) were generated at the beginning (pre-tetanus) and the end (post-tetanus) of the experiment. The pre-tetanus I/O stimulation intensities for each subject ranged from intensities that were subthreshold for PS generation to those that produced an asymptotic PS.

Two measures, the PS amplitude and excitatory postsynaptic potential (EPSP) slope, were extracted from averaged I/O responses that had a pre-tetanus PS amplitude of approximately 4 mV (these responses were generally located midway on the I/O function). To determine the occurrence of LTP, each measure was submitted to a one-way analysis of variance with treatment group as a four level factor.

Administration of drugs

Two groups of animals received i.p. injections of ketamine (30 mg/kg), a non-competitive NMDA antagonist which blocks the induction of LTP in the dentate gyrus of anesthetized rats[23]. One group (Theta/Ket; n = 3) of animals received TBS 15 min following the drug injection, the other group (Sham/Ket; n = 3) received no electrical stimulation.

Ligand-binding autoradiography

One hour following stimulation (TBS or LF), the rats were decapitated, their brains rapidly removed, frozen in –20°C methylbutane, and stored at –70°C until sectioning. Frontal sections (10 μm thick) were cut at –15°C in a cryostat. The sections were thaw mounted on chrome-alum/gelatin-coated slides, and stored at –70°C.

For [^{3}H]TCP binding (spec. act., 47.8 Ci/mmol; NEN Dupont, DE), slides were equilibrated to room temperature and preincubated in 100 mM HEPES, 50 μM EGTA, 10 μM glutamate, and 10 μM glycine at 35°C for 30 min. Sections were then incubated at room temperature in the same buffer containing 100 nM [^{3}H]TCP for 45 min with or without 5 mM ketamine. Slides were rinsed at room temperature twice (10 s per rinse) in 100% buffer and once (5 s) in 50% buffer, dipped 3 times in distilled water, and rapidly dried under a stream of warm air. Non-specific binding represented < 15% of total binding.

[^{3}H]AMPA binding (spec. act., 29.2 Ci/mmol; NEN Dupont, DE) was performed according to a modification of Olsen et al.[31]. After equilibration to room temperature, slides were preincubated in Tris/acetate buffer (100 mM, pH = 7.2–7.4) containing 100 mM potassium thiocyanate and 100 μM EGTA for 30 min at 35°C. Sections were then incubated at 0–4°C for 45 min in the same buffer containing 400 nM [^{3}H]AMPA with or without 1 mM quisqualate. Slides were rinsed and dried as for the TCP binding, except rinses were performed at 0–4°C. Non-specific binding represented <10% of total binding.

Autoradiographic film (Hyperfilm, Amersham, IL) was pressed against the tissue sections on the slides and against radioactive standards (ARC, St. Louis, MO). After exposure for 10–15 days, the films were developed for 3–5 min at room temperature in Kodak GBX developer and fixer.

Analysis of autoradiographs

The autoradiographs were analyzed with an image analysis system (Dumas from Drexel University) to determine the amount of binding in nine different brain regions (CA1 oriens, CA1 radiatum, CA3 oriens, CA3 radiatum, dentate gyrus (molecular layer), hilus, external cortex (layers I and II), internal cortex (layers III–VI) and thalamus; Fig. 2). Optical density measurements were made in each hemisphere on adjacent coronal sections. The measures were averaged across the sections and converted to pmol/mg protein of bound ligand.

Statistical analysis

The transformed ligand binding data were submitted to a multivariate factorial repeated measures analysis of variance (mixed model) with factors of treatment group, side (2 levels: left hemisphere and right hemisphere) and brain region (9 levels: see above); independent MANOVAs were performed on the AMPA and TCP data. Planned comparisons in the form of univariate F-tests were carried out following significant omnibus F-tests.

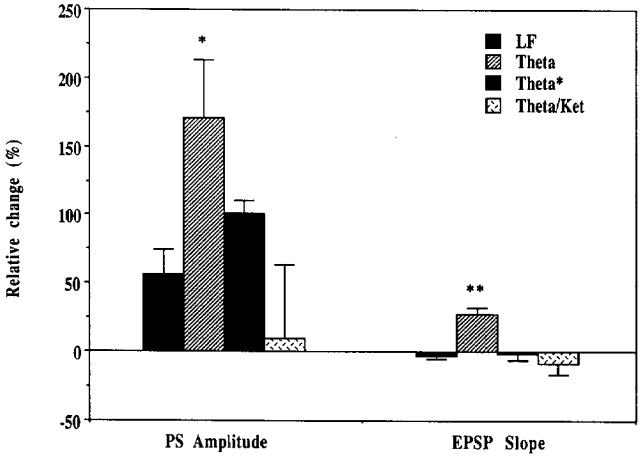

Fig. 1. Percent change from baseline in PS amplitude and EPSP slope for the 4 treatment groups. Values are expressed as means ± standard error of the mean (S.E.M.). The single asterisk indicates that the Theta group significantly differed ($P < 0.05$) from both the Theta/Ket and LF groups; double asterisks indicate that the Theta group significantly differed from all the other treatment groups. None of the remaining treatment groups (Theta*, Theta/Ket, or LF) significantly differed from one another.

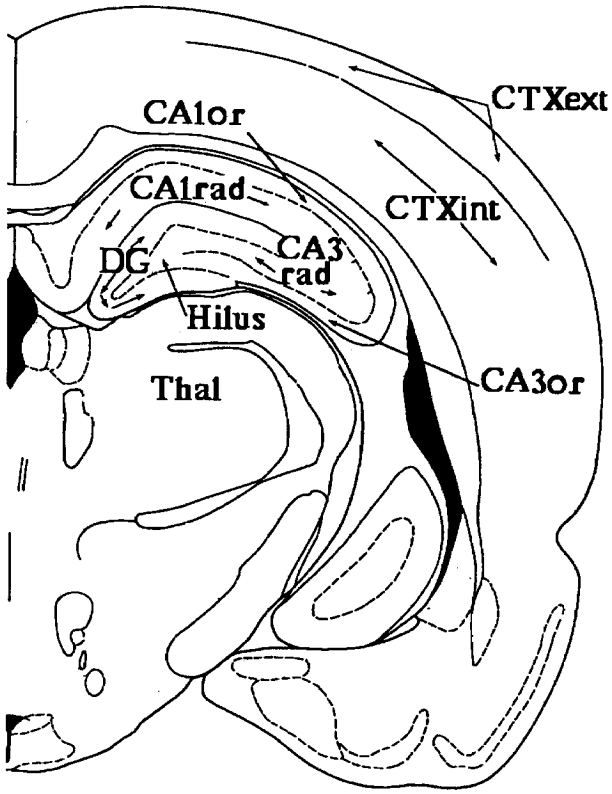

Fig. 2. Schematic diagram of a coronal section showing the brain regions that were quantitated. CA1 and CA3, hippocampal cell layers (or, stratum oriens; rad, stratum radiatum/lacunosum); DG, molecular layer of the dentate gyrus; CTXint, inner layers of cortex; CTXext, outer layers of cortex; Thal, dorsal thalamic nuclei; Hilus, dentate hilus.

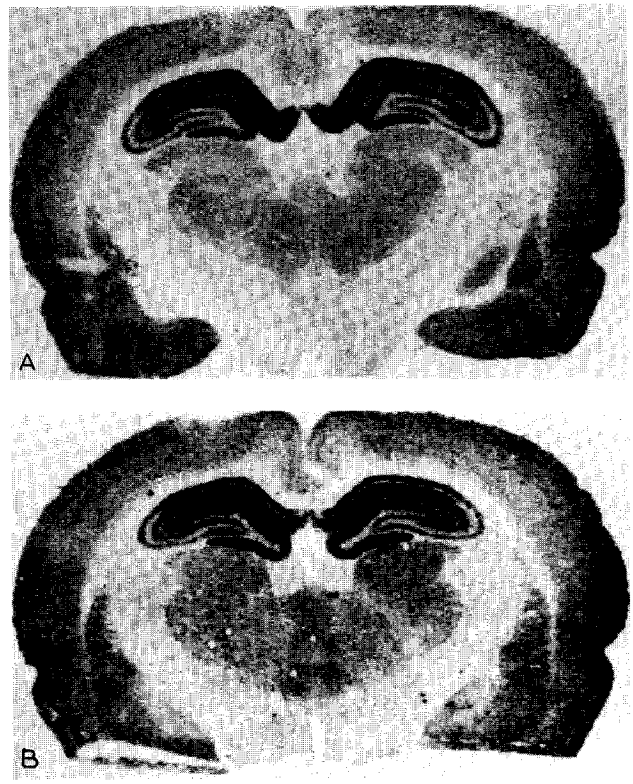

Fig. 3. Autoradiograms obtained from slices incubated with [^{3}H]TCP. A: section from an animal that received low intensity TBS (Theta) and showed LTP; B: section from an animal that received low-frequency stimulation (LF) and did not show LTP. The brain sections were mounted on the same slide and therefore processed together during the entire procedure

RESULTS

Electrophysiology

Fig. 1 represents the mean percent change from baseline in PS amplitude and EPSP slope for 4 treatment groups. The ANOVA revealed significant differences between the treatment groups in both PS amplitude ($F_{2,15} = 4.00$, $P < 0.03$) and EPSP slope ($F_{2,15} = 13.82$, $P < 0.0003$). Individual comparisons ($P < 0.05$) of the PS amplitude means indicated that animals receiving low intensity TBS (Theta group) significantly differed from both low-frequency controls and ketamine-treated subjects (indicated with a single asterisk on Fig. 1). Comparisons of the EPSP slope means indicated that subjects in the Theta group significantly differed from those in the remaining groups (indicated by double asterisks in Fig. 1). Therefore, only animals receiving low intensity TBS exhibited LTP.

NMDA receptor binding

Fig. 3 represents typical [^{3}H]TCP autoradiograms obtained from a rat which received low intensity TBS and expressed LTP (Fig. 3A), and from a rat which received low-frequency stimulation and did not express LTP (Fig.

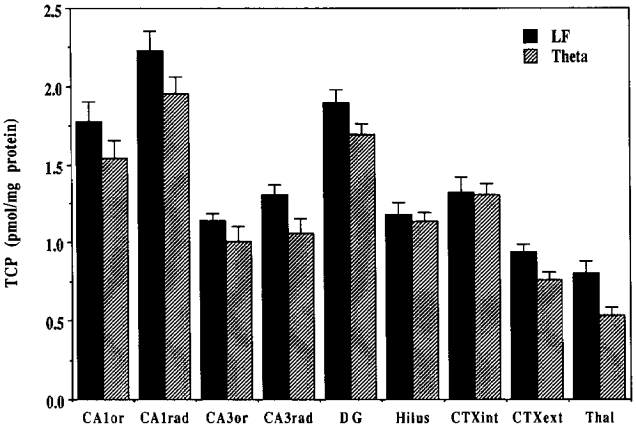

Fig. 4. Effect of perforant path stimulation on ^{3}H]TCP binding. Values represent optical densities converted to pmol/mg of protein that were measured from the autoradiograms (similar to those shown in Fig. 3) obtained from two groups of animals. One group received low intensity TBS (Theta), and the other low-frequency stimulation (LF) to the perforant path (see Materials and Methods). The regions analysed correspond to the ones depicted in Fig. 2. The values are expressed as means ± S.E.M.

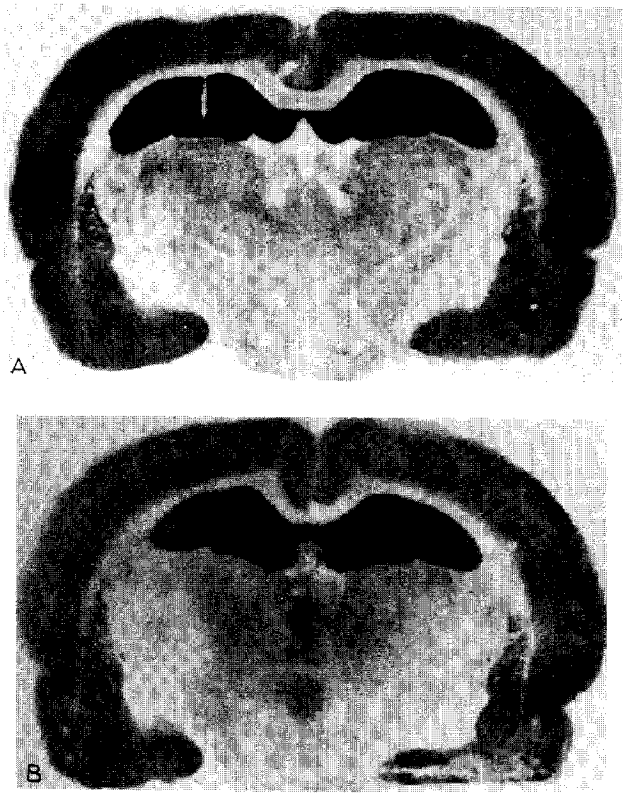

Fig. 5. Autoradiograms obtained from slices incubated with ^{3}H]AMPA. The brain sections were obtained at the same time on the same slide and therefore processed together during the whole procedure A: section from an animal which had received low intensity TBS (Theta) and showed LTP; B: section from an animal which had received low-frequency stimulation (LF) and therefore did not show LTP. Note the recording electrode track visible on section A.

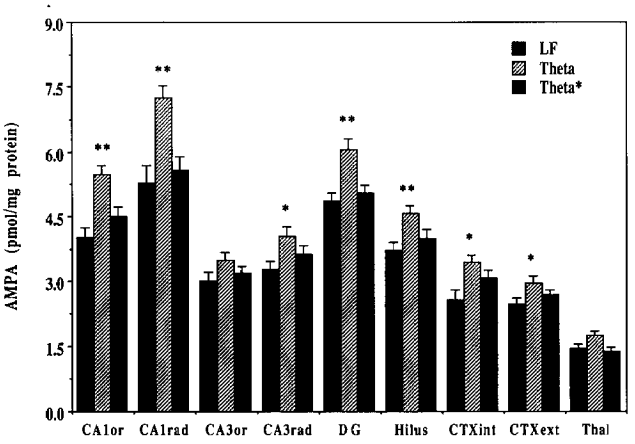

Fig. 6. Effect of perforant path stimulation on [^{3}H]AMPA binding. Values (means ± S.E.M.) represent optical densities converted to pmol/mg of protein that were measured from autoradiograms (similar to those shown in Fig. 4) obtained from 3 groups: Theta, low intensity TBS; Theta*, high intensity TBS; LF, low-frequency stimulation. The regions analyzed correspond to the ones depicted in Fig. 2. Single asterisks indicate regions in which the Theta group significantly differed ($P < 0.05$) from the LF group. Double asterisks indicate regions in which the Theta group statistically differed ($P < 0.05$) from both the LF and Theta* groups. No differences between the Theta* and LF groups were evident in any of the brain regions.

3B). TCP binding was not significantly lateralized in any of the treatment groups (Theta and LF) as indicated by a non-significant interaction between the factors of group, side, and region ($F_{8,72} = 0.57$; $P = 0.80$), and a non-significant interaction between the factors of group and side ($F_{1,9} = 0.53$; $P = 0.49$). MANOVA revealed no differences between these groups (Fig. 4) in the magnitude of TCP binding in the various brain regions ($F_{8,72} = 1.87$; $P = 0.08$). No difference in [^{3}H]TCP binding between any of the other treatment groups was detected.

AMPA receptor binding

Fig. 5 represents a typical [^{3}H]AMPA autoradiogram obtained from a rat that received low intensity TBS and expressed LTP (Fig. 5A), and from a rat which received low-frequency stimulation and did not express LTP (Fig. 5B). No significant differences in the distribution of AMPA binding between the Sham and LF groups were revealed by the MANOVA; therefore the LF group was used for all subsequent comparisons. Surprisingly, none of the treatment groups showed significant differences in the laterality of AMPA binding. This was indicated by a non-significant interaction between the factors of group, side and region ($F_{16,112} = 1.14$; $P = 0.33$), and a non-significant interaction between the factors of group and side ($F_{2,14} = 0.50$; $P = 0.62$). Fig. 6 shows the quantification of the effect of different perforant path stimulations on tritiated AMPA binding. A significant interaction between the factors of group and region revealed

that the groups differed with respect to the levels of AMPA binding in the brain regions quantitated ($F_{16,112} = 4.78$; $P < 0.00001$). Planned comparisons ($P < 0.05$) revealed that subjects in the Theta group, but not those in the Theta* group (high intensity TBS, no LTP), had significantly more AMPA binding in hippocampal (CA1 oriens, CA1 radiatum, CA3 radiatum, dentate gyrus and hilus) and cortical regions relative to animals in the LF group (the regions marked with an * in Fig. 6). Further comparisons revealed that subjects in the Theta group differed from those in the Theta* group only in hippocampal areas: CA1 oriens, CA1 radiatum, dentate gyrus and hilus (the regions marked by ** in Fig. 6). No differences were found for CA3 oriens and thalamus. Increased AMPA binding was found only in rats (Theta group) that exhibited LTP.

To determine if the increased level of AMPA binding observed in animals exhibiting LTP was associated with NMDA receptor activation, ketamine, a non-competitive NMDA receptor antagonist which blocks the induction of LTP in the dentate gyrus of anesthetized rats[23], was administered to a group of 3 animals receiving TBS (Theta/Ket). As shown in Fig. 1, LTP induction was prevented in animals treated with ketamine. A second group of animals was administered ketamine but did not receive any electrical stimulation (Sham/Ket). A non-significant interaction between the factors of group and region ($F_{8,32} = 0.27$; $P = 0.85$) indicated that the Theta/Ket group did not differ from the Sham/Ket group with respect to the magnitude of AMPA binding in any of the brain regions quantitated. Thus, ketamine administration blocked both the induction of LTP and the increase in AMPA binding in response to tetanic stimulation.

DISCUSSION

The results of the present study reveal that the induction of long-term potentiation in perforant path-granule cell synapses of anesthetized rats is associated with an increase in [^{3}H]AMPA binding. The increase in AMPA binding was not restricted to the dentate gyrus, and was not specific to the hemisphere ipsilateral to perforant path stimulation, but was correlated with LTP in the ipsilateral tetanized pathway.

The central issue at hand is whether or not the increased AMPA binding observed in the present study represents a biochemical correlate of LTP. Two pieces of evidence support this possibility: first, animals that received high intensity TBS did not exhibit LTP, and did not exhibit increases in AMPA binding in any brain region quantitated. Second, animals treated with the NMDA antagonist ketamine exhibited neither LTP nor an increase in AMPA binding. Therefore, increased AMPA binding only occurred in subjects exhibiting LTP.

One might argue that the increase in AMPA binding observed in hippocampal regions contralateral to the side of perforant path stimulation cannot be associated with LTP per se, because it violates a fundamental property of LTP, that is, synapse specificity. In other words, only the tetanized pathways would be expected to exhibit LTP and, thus, increased AMPA binding. The present findings constrain us to one explanation: tetanization of the perforant path ultimately results in the establishment of heterosynaptic potentiation in other, non-tetanized, hippocampal pathways. Indeed, perforant path tetanization results in monosynaptic LTP in both CA3 and CA1 ipsilateral to the site of stimulation[42]. It may be the case that plasticity established in these regions is then 'transferred' via commissural pathways to the contralateral hippocampus.

An alternative explanation for the present findings is that the changes in glutamate receptor binding are due to seizure activity induced by the high-frequency TBS. Two points argue against this interpretation: first, pharmacologically induced limbic seizures are associated with massive, bilateral activation of several immediate early genes (IEGs), including c-*fos* and *zif/268*, in the dentate gyrus[11,26,41]. In contrast, we have found that the stimulation parameters used in the present study are not associated with an increase in IEG mRNAs in the dentate gyrus[10,34]. Second, both kindling- and kainic acid-induced seizures are associated with a decrease in AMPA binding[13,24].

A third interpretation of the present data would be that the changes in AMPA binding represent a generalized neural response to high-frequency intracranial electrical stimulation. However, rats receiving high intensity TBS (Theta*) did not exhibit either LTP or increased AMPA binding in any of the brain regions examined. Therefore, high-frequency stimulation in and of itself is not responsible for the increase in AMPA binding observed in animals in the Theta group.

Assuming that the changes in AMPA receptors we observed in the present study are in fact associated with LTP, it would be the first demonstration that changes in the binding properties of postsynaptic receptors accompany LTP. Somewhat surprisingly, our results are at variance with a report which failed to detect changes in AMPA binding in membranes prepared from potentiated hippocampal slices[20]. However, the difficulty of potentiating a large number of synapses in a slice preparation, on one hand, and the possible existence of extrasynaptic receptors in a membrane preparation, on the other hand, may have precluded the detection of small changes in binding. With regards to the present data, it is not known whether the increase in AMPA

binding is due to an increase in the number or the affinity of AMPA receptors. The relatively rapid change in the binding properties of the receptors (≤1 h), and a recent report indicating that phospholipase A_2 (PLA_2), a calcium-dependent lipase which increases the affinity of AMPA receptors, may be involved in the establishment of LTP[24], lead us to believe that the increase in AMPA binding was most likely due to a modification of receptor affinity. Calcium influx through open NMDA receptor-gated channels may initiate an enzymatic cascade capable of modifying postsynaptic receptors in such a manner.

In summary, we have found that the induction of LTP in the rat dentate gyrus in vivo results in a significant increase in AMPA binding in several subregions of the hippocampus. The increase in binding was dependent on NMDA receptor activation, was bilateral, and was not solely due to high-frequency activation of granule cells. Together with previous reports[9,12,24,29,35], these results provide compelling evidence for a role of AMPA receptors in the expression of LTP. Further experiments must be carried out to determine if the change in AMPA receptors persists in parallel with LTP, and if it correlates with electrophysiological parameters.

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