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Effects of ketamine on synaptic transmission and long-term potentiation in layer II/III of rat visual cortex in vitro

Mahmoud Salami [a,*], Yaghoub Fathollahi [b,c], Hossein Esteky [a], Fereshteh Motamedi [a], Nafiseh Atapour [d]

[a] *Department of Physiology, School of Medicine, Shaheed Beheshti University of Medical Science, Tehran, Iran*
[b] *Department of Physiology, School of Medical Sciences, Tarbiat Modarres University, Tehran, Iran*
[c] *Institute of Biochemistry and Biophysics, University of Tehran, Tehran, Iran*
[d] *Neuroscience Research Center, Kerman University of Medical Sciences, Kerman, Iran*

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Abstract

The effects of ketamine, which has NMDA receptor antagonist properties, on synaptic transmission and long-term potentiation in layer II/III of adult rat visual cortex were examined in vitro. Field potentials were recorded in layer II/III following layer IV stimulation. Primed-burst stimulation was used for induction of long-term potentiation. Stimulation of layer IV resulted in a two-component response in layer II/III, a population excitatory postsynaptic potential1 (EPSP1) and a population excitatory postsynaptic potential2 (EPSP2). DL-2-Amino-5-phosphono-valeric acid (AP5), a competitive NMDA receptor antagonist, reduced the amplitude of the population EPSP1 while ketamine increased the amplitude of the population EPSP2. The results showed that primed-burst stimulation induced long-term potentiation in layer II/III of the visual cortex in vitro. Preincubation for 30 min with AP5 (25–100 μM) reduced the extent of long-term potentiation of the population EPSP2 and blocked the induction of long-term potentiation of the population EPSP1. When ketamine (100–200 μM) was present for 30 min prior to tetanic stimulation, it blocked the induction of long-term potentiation of the population EPSP1 and reduced the extent of long-term potentiation of the population EPSP2. We conclude that ketamine can interfere with synaptic transmission in the visual cortex. Primed-burst stimulation is an effective protocol for neocortical potentiation. NMDA receptors are involved in the induction of long-term potentiation by primed-burst stimulation of the population EPSP1 and population EPSP2 in adult rat visual cortex in vitro.

Keywords: Synaptic plasticity; Long-term potentiation; Primed-burst stimulation; Visual cortex; Ketamine

1. Introduction

It has long been assumed that lasting modifications of synaptic transmission form a basis for information storage in the nervous system, and that modifications subserving certain forms of learning and memory are likely to reside in the cerebral neocortex (Hebb, 1949). Since the initial discovery of long-term potentiation by Bliss and Lømo (1973), the process has been studied intensively in the hippocampus (Bliss and Collingridge, 1993). Long-term potentiation has also been investigated, although less intensively, in the neocortex particularly in the visual cortex.

According to present evidence, very similar mechanisms mediate synaptic plasticity in the hippocampal CA1 area and the visual cortex. The visual cortex offers an important, perhaps unique, advantage over the CA1 for the eventual understanding of how long-term potentiation and long-term depression contribute to the functioning of the brain. This advantage is that the visual cortex lies much closer to the interface between electrophysiology and behavior than does the hippocampus (Kirkwood and Bear, 1995).

Electrical stimulation of white matter, intracellular recordings (Sutor and Hablitz, 1989), and field potential recordings (Aroniadou and Teyler, 1991) have shown that there are two types of excitatory postsynaptic potentials (EPSPs) in layer II/III of the visual cortex: a low-threshold and short latency EPSP and a high-threshold and long latency EPSP, which are called excitatory postsynaptic

* Corresponding author. Institute of Biochemistry and Biophysics, Tehran University, PO Box 13145-1384, Tehran, Iran. Fax: +98-21-640-4680.

E-mail address: salami@ibb.ut.ac.ir (M. Salami).

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potential1 (EPSP1) and excitatory postsynaptic potential2 (EPSP2), respectively. The EPSP1 is a monosynaptic response and, in turn, it includes EPSP1a and EPSP1b, which are mediated by non-NMDA and NMDA receptors, respectively. The EPSP2 is probably a polysynaptic response and present evidence indicates that NMDA receptor-dependent and -independent EPSP2 can exist (Aroniadou and Teyler, 1991). In addition, inhibitory postsynaptic potentials (IPSP) have been demonstrated in layer II/III of the visual cortex including a fast IPSP and a slow IPSP that are mediated by $GABA_A$ and $GABA_B$ receptors, respectively (Connors et al., 1988).

Previous studies have generally emphasized that long-term potentiation cannot readily be elicited in the visual cortex from adult rats, especially in the absence of a GABA blocker (Artola and Singer, 1987; Kimura et al., 1989; Kato et al., 1991). Application of high-frequency electrical stimulation to the pathway of interest can induce long-term potentiation. Among the different patterns of tetanic stimulation, theta-burst stimulation and primed-burst stimulation may particularly be important. These protocols mimic the synchronized firing patterns at frequencies that occur in the hippocampus of rats during learning (Bliss and Collingridge, 1993), but it is not clear whether this is also true for the visual cortex. However, experimental data indicate that theta-burst stimulation is an effective stimulation protocol for neocortical potentiation (Kirkwood and Bear, 1994; Castro-Alamancos and Connors, 1996).

It has been shown that NMDA receptors are involved in neocortical long-term potentiation. Artola and Singer (1990) found that NMDA receptor-specific antagonists are able to block long-term potentiation of the EPSP. Findings of different laboratories show that DL-2-amino-5-phosphono-valeric acid (AP5), an NMDA receptor antagonist, inhibits NMDA receptor-mediated long-term potentiation (Kimura et al., 1989; Artola and Singer, 1990; Lee et al., 1991; Bear et al., 1992). However, Komatsu et al. (1991) reported that tetanic stimulation in the presence of AP5, in some cases, led to long-term potentiation; 6,7-dinitroquinoxaline-2,3(1*H*,4*H*)-dione (DNQX), a non-NMDA receptor antagonist, eliminated this potentiation. This type of potentiatoin has also been reported by Aroniadou and Teyler (1991).

Ketamine (2-*O*-chlorophenyl-2-methylaminocyclohexanone), which is pharmacologically similar to MK-801, blocks NMDA receptors in a use-dependent mode and the blockade is enhanced by the presence of agonist (Gonzales et al., 1995). It blocks NMDA receptors in closed and open states (Orser and Freeman, 1997). This action is thought to contribute to potent anesthetic and analgesic properties of ketamine (Irifune et al., 1992). Ketamine can also interfere with synaptic consolidation in the visual cortex (Rauschecker et al., 1990) and inhibits NMDA receptor-dependent EPSP in the cerebral cortex (Thomson et al., 1985). It also blocks glutamate receptors that are activated by quisqualate (Gonzales et al., 1995). But AP5 is a competitive NMDA receptor antagonist that acts on the transmitter recognition site of the receptor and prevents receptor activation by competing with the agonist for the transmitter-binding site (MacDonald and Nowak, 1990).

Until now, the effects of ketamine on long-term potentiation in the visual cortex have not been established. Therefore, the effects of ketamine on the induction and maintenance of long-term potentiation induced by primed-burst stimulation in the visual cortex were investigated in vitro.

2. Materials and methods

2.1. Animals

Visual cortex slices were prepared from male and female NMRI rats ranging from 4–6 weeks of age. As long-term potentiation was found to be unrelated to the sex of the animal (Berry et al., 1989), data from the two sexes were pooled. Fifteen slices from 12 rats and 14 slices from 10 rats were used in control and ketamine experiments, respectively. Animals were housed in a standard environment on a 12:12 h light/dark cycle at 22 ± 2°C. Animals were allowed access to water and food ad libitum.

2.2. Slice preparation

Slices were obtained from the primary visual cortex of male or female rats. Animals were anesthetized with ether and then decapitated. The brain was rapidly removed and placed into cold (2–4°C) oxygenated artificial cerebrospinal fluid (containing in mM: NaCl, 124; $CaCl_2$, 2; $MgCl_2$, 2; KH_2PO_4, 1.2; $NaHCO_3$, 26; glucose, 10). A block of the brain including the primary visual cortex was placed on a vibroslice instrument and 400–450 μm thick slices were cut. Slices used for recording were rapidly transferred to an interface type recording chamber where they were maintained at the liquid/gas interface with an atmosphere of humidified 95% O_2 and 5% CO_2. Slices were perfused with 32 ± 2°C artificial cerebrospinal fluid at a flow rate of 2 ml/min and incubated for 1 h or more before beginning of an experiment.

2.3. Electrophysiology

Field potentials were recorded from layer II/III (400–500 μm below the cortical surface) using a glass micropipette filled with NaCl (2 M) solution, yielding impedances of 2.0–5.0 MΩ. A monopolar recording configuration was used with the slice pool grounded. The recorded neural signal was amplified, filtered from 0.1 Hz to 5 kHz, and digitized at 10 kHz using a customized program on an IBM-AT compatible computer.

The stimulus test pulses were delivered through a bipolar electrode (twisted pair of teflon-coated stainless steel

wire) at two fixed intensities of 25 and 200 μA in layer IV of visual cortex. Pulse width (200 μs) was the same for each slice. Slices that exhibited a threshold greater than 25 μA were considered unhealthy and were not used for recording. Before tetanus was delivered, the average evoked field potentials were required to be stable for 30 min. When the variation in field potential amplitude was less than ±10% for 30 min, the baseline recordings were considered stable. Responses were recorded before, 30 and 60 min after tetanic stimulation. In the experiments in which ketamine (100 μM; Parke-Davis), a non-competitive NMDA receptor antagonist and AP5 (25–100 μM; Aldrich), a competitive NMDA receptor antagonist, were used, the baseline recordings were obtained before and 30 min after application of the drugs (slices were perfused with medium containing ketamine or AP5). At 30 and 60 min after tetanus, field potentials of layer II/III were also recorded at the above-mentioned two fixed stimulus intensities. For induction of long-term potentiation, primed-burst stimulation was delivered which consisted of eight primed-burst per stimulation. Each primed-burst consisted of a single priming pulse followed 170 ms later by a burst (10 pulses at 100 Hz) of test pulses at 200 μA stimulus intensity. Primed-bursts were delivered with an interval of 10 s.

2.4. Data analysis

Extracellular field potentials recorded in layer II/III consists of two population EPSPs: a population EPSP1 and a population EPSP2. The amplitude of population EPSPs (from the beginning of negative wave to its peak in mV) was measured from averaged waveforms for pre- and post-tetanic stimulation recordings. Then the amplitude of each component was expressed as a percentage of its average amplitude before the primed-burst stimulation at each stimulus intensity. Slices in which the post-tetanus population EPSP amplitude was at least 20% higher than the average baseline population EPSP amplitude were said to demonstrate long-term potentiation, whereas a post-tetanic decrease in population EPSP amplitude greater than 20% indicated long-term depression. All data are expressed as means ± S.E.M. Analysis of variance (repetitive measures for comparison between the various times within each group and completely randomized for comparison between different groups) followed by Tukey's test and paired *t*-test was used for statistical analysis. Results were considered significant at the level of $P < 0.05$.

3. Results

3.1. Baseline recording in layer II / III of visual cortex

Stimulation of layer IV resulted in a two-component response in layer II/III at 25 μA stimulus intensity. Both components were eliminated in Ca^{2+}-free medium (Fig. 1). The first component had a short latency (1.25 ± 0.11 ms) and high amplitude (2 ± 0.3 mV) and the second component had a long latency (3.94 ± 0.23 ms) and low amplitude (0.9 ± 0.2 mV). A high stimulus intensity (200 μA) differently influenced the baseline response. Whereas the amplitude of the first component increased without exception, the amplitude of the second component appeared reduced or showed a little change. Therefore, the response components were called population EPSP1 and population EPSP2, respectively (Fig. 2).

3.2. Induction of long-term potentiation of population EPSPs

After a suitable baseline period, induction of long-term potentiation was attempted using primed-burst stimulation. Tetanic stimulation in layer IV induced long-term potentiation in both population EPSPs at 25 μA stimulus intensity. Long-term potentiation was observed in 8 of 15 slices and the amplitude of the population EPSP1 was potentiated by about 23.19 ± 9.8%. The potentiation was sustained for 60 min after primed-burst stimulation (Fig. 2A and Fig. 3A) and recognized as long-term potentiation [$F(2,41) = 3.98$, $P < 0.05$]. The extent of long-term potentiation of the population EPSP2 was greater (120.75 ± 41.85%) than that of the population EPSP1 [$F(2,12) = 8$, $P < 0.01$] in 12 of 15 (Fig. 2A and Fig. 3B). A high stimulus intensity (200 μA) did not significantly affect long-term potentiation of the population EPSP1 (7 of 15 slices, Fig. 4A), while it markedly decreased long-term potentiation of the population EPSP2 (5 of 14 slices, Fig. 4B).

3.3. Effect of AP5 on long-term potentiation of population EPSPs

The experiments were performed with a preincubation of AP5 for longer than 30 min to allow the effect on baseline responses to reach equilibrium. At 25 μA stimu-

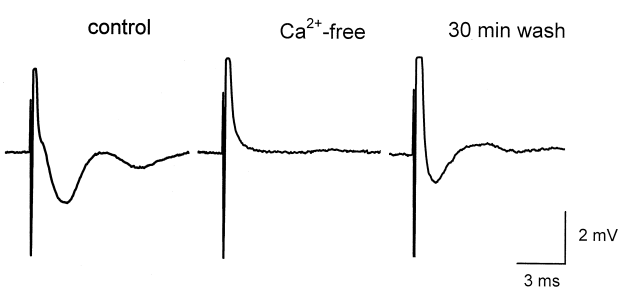

Fig. 1. The response components elicited in layer II/III in response to layer IV stimulation in normal medium, Ca^{2+}-free medium and after 30 min washout with normal medium. Notice that both components were eliminated in Ca^{2+}-free medium and almost fully recovered after a 30-min washout.

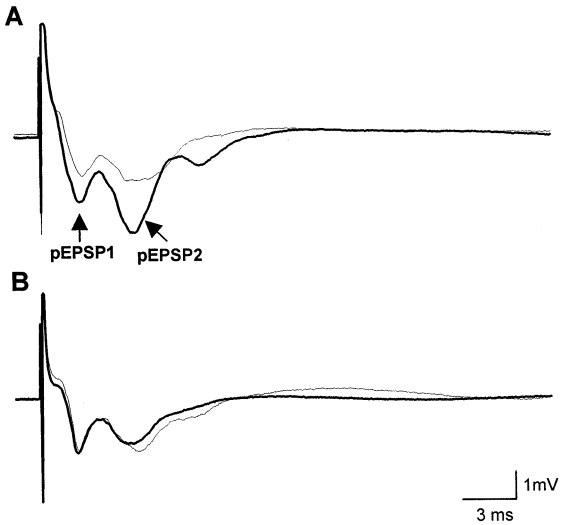

Fig. 2. Representative superimposed responses from control (A) and ketamine-treated (B) slices before (thin line) and after 60 min (thick line) of primed-burst stimulation, at 25 μA stimulus intensity.

lus intensity, AP5 (25–100 μM) significantly depressed the amplitude of the population EPSP1 ($P < 0.05$, paired *t*-test), but not that of the population EPSP2 (Fig. 5). AP5 abolished the induction of long-term potentiation of the population EPSP1 while it reduced slightly the extent of long-term potentiation of the population EPSP2.

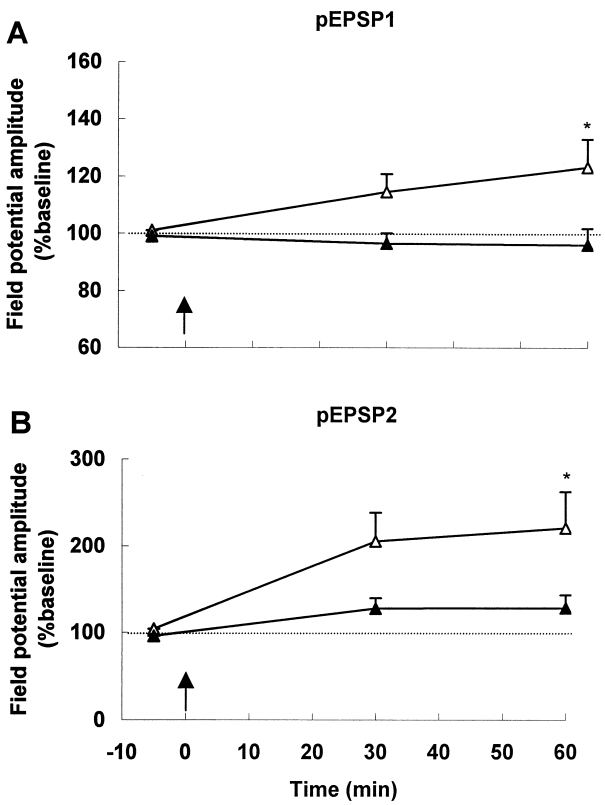

Fig. 3. Percentage change in amplitude of population EPSP1 (A) and population EPSP2 (B) in control (open triangle) and ketamine-treated (closed triangle) slices at 25 μA stimulus intensity, 30 and 60 min after primed-burst stimulation. The data are shown as means ± S.E.M. The differences were significant with analysis of variance followed by Tukey's test. Arrow indicates application of primed-bursts stimulation. $^{*}P < 0.05$.

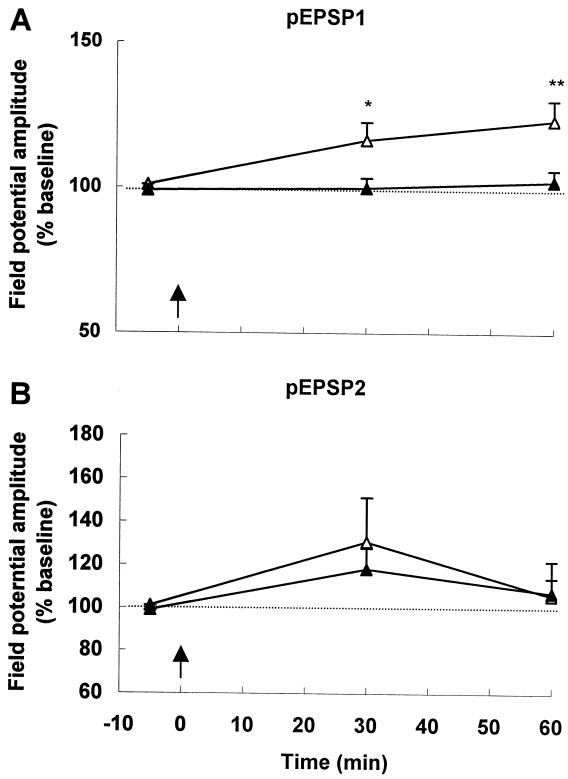

Fig. 4. Percentage change in the amplitude of population EPSP1 (A) and population EPSP2 (B) in control (open triangle) and ketamine-treated (closed triangle) slices at 200 μA stimulus intensity, 30 and 60 min after primed-burst stimulation. The data are shown as means ± S.E.M. The differences were significant with analysis of variance followed by Tukey's test. Arrow indicates application of primed-burst stimulation. $^{*}P < 0.05$, $^{**}P < 0.01$.

3.4. Effect of ketamine on long-term potentiation of population EPSP1

Perfusion of the slices for 30 min with medium containing 100 μM ketamine increased the amplitude of the baseline response at 25 μA stimulus intensity (Fig. 6A). Incubations with ketamine were able to completely block the induction of long-term potentiation of the population EPSP1, so that 60 min after tetanic stimulation, long-term potentiation appeared only in 1 of 14 slices (Fig. 2B). The difference between ketamine-treated and control slices was generally significant [$F(1,49) = 10.5$, $P < 0.05$]. Fig. 3A shows the mean normalized population EPSP1 amplitude versus time for both groups of slices. Also ketamine significantly blocked the potentiation of the population EPSP1 at 200 μA stimulus intensity [$F(1,49) = 13.34$, $P < 0.0007$] (Fig. 4A). Long-term potentiation was elicited only in 1 of 13 slices.

3.5. Effect of ketamine on long-term potentiation of population EPSP2

Perfusion of the slices with artificial cerebrospinal fluid containing ketamine increased the amplitude of the baseline response considerably ($P < 0.015$, Fig. 6B). In the ketamine-treated slices, primed-burst stimulation induced potentiation of the amplitude of the population EPSP2 at 25 μA stimulus intensity. Nevertheless, the extent of potentiation was markedly lower than that of control slices (Fig. 2B). Statistical analysis showed that the difference between the two groups was generally significant [$F(1,51) = 8.39$, $P < 0.05$]. It is important to note that, in control slices, potentiation increased with elapsing of time after tetanus whereas this phenomenon was not observed in the ketamine-bathed slices (Fig. 3B). Ketamine did not affect long-term potentiation of the population EPSP2 at 200 μA stimulus intensity (Fig. 4B).

When the ketamine concentration was raised from 100 to 200 μM, the response amplitude did not significantly change in either population EPSP.

Following washout of ketamine for 30 min, the same stimulus protocol resulted in long-term potentiation in some cases.

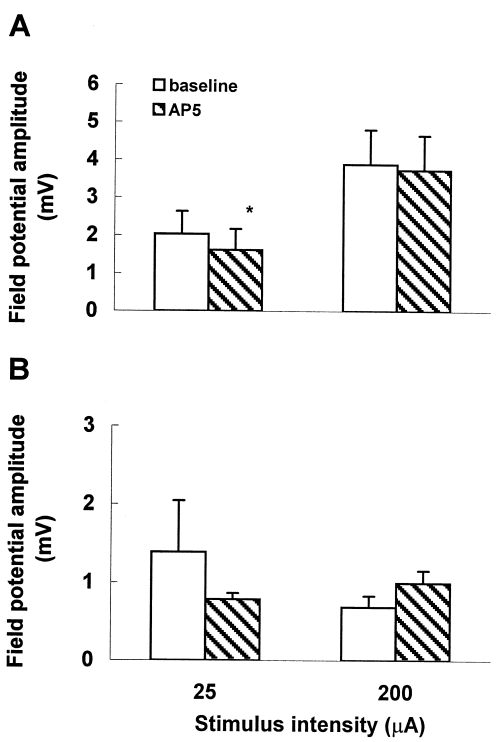

Fig. 5. Effects of AP5 on the population EPSPs in control medium at two stimulus intensities of 25 and 200 μA. Population EPSPs recorded in response to layer IV stimulation before (baseline) and during application of 100 μM AP5. These results are representative of six slices. (A) Effect of AP5 on the amplitude of the population EPSP1. AP5 reduced the amplitude of the population EPSP1 significantly. (B) Effect of AP5 on the amplitude of the population EPSP2. AP5 reduced the amplitude of population EPSP2 but not significantly. $^{*}P < 0.05$.

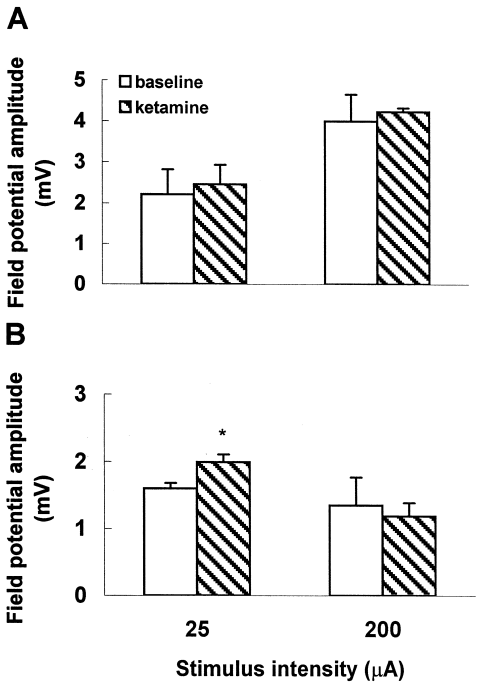

Fig. 6. Effects of ketamine on the population EPSPs in control medium at two stimulus intensities of 25 and 200 μA. Population EPSPs recorded in response to layer IV stimulation before (baseline) and during application of 100 μM ketamine. These results are representative of six slices. (A) Effect of ketamine on the amplitude of the population EPSP1. Ketamine increased the amplitude of the population EPSP1 but not significantly. (B) Effect of ketamine on the amplitude of the population EPSP2. Ketamine increased the amplitude of the population EPSP2 significantly. $^{*}P < 0.05$.

Our results indicated that the incidence of long-term depression was similar in the ketamine-treated and control slices for both population EPSPs.

4. Discussion

4.1. Baseline recordings

The analysis of field potential data has been rigorously discussed in the literature (Berry et al., 1989; Aroniadou and Teyler, 1991; Aizenman et al., 1996; Castro-Alamancus and Connors, 1996). We used field potentials to assess the effect of ketamine on the plasticity of synaptic connections in layer II/III of rat visual cortex in vitro, in response to primed-burst stimulation, as a type of activity pattern, that is extensively used to study the plasticity of synaptic connections in the hippocampal CA1 area.

Stimulation of layer IV resulted in a two-component response. We believe that the response components that we designate as field potentials represent the synchronized activity of a population of neurons, because the amplitudes of these responses were graded with respect to stimulus intensity. To determine which response components did not depend on synaptic transmission, we examined re-

sponses in slices maintained in Ca^{2+}-free medium. Both components were eliminated in Ca^{2+}-free medium. In some cases, non-synaptic activity was present at a shorter latency than that of the first component. Therefore, we named these components population EPSP1 and population EPSP2, according to their characteristics. Similar waveforms have also been reported following white matter stimulation (Aroniadou and Teyler, 1991). In addition, current source density (CSD) analysis has shown that stimulation of both sites produces a CSD profile that is quite similar (Aizenman et al., 1996).

A high stimulus intensity (200 μA) increased the amplitude of the population EPSP1, but the mean amplitude of the population EPSP2 was decreased. Since the EPSP2 coincided with the fast IPSP, which is activated at high stimulus intensity (Sutor and Hablitz, 1989; Luhmann and Prince, 1990), it can be said that the fast IPSP decreased the amplitude of the population EPSP2 at high stimulus intensity.

The competitive NMDA receptor antagonist, AP5, reduced the amplitude of the population EPSP1, suggesting that it was, in part, mediated by NMDA receptors. This result is consistent with the following findings. The EPSP has been examined in layer II/III of the visual cortex. The EPSP is divided into two components: an early EPSP (or EPSP1) and a late EPSP (or EPSP2). The EPSP1 is a monosynaptic response and, in turn, it includes EPSP1a and EPSP1b components that are mediated by non-NMDA and NMDA receptors, respectively. The EPSP2 probably is a polysynaptic response and present evidence shows that a NMDA receptor-dependent and -independent EPSP2 can exist (Aroniadou and Teyler, 1991).

Ketamine, which has NMDA receptor antagonist properties, did not have a considerable effect on the amplitude of the population EPSP1, but increased the amplitude of the population EPSP2. The mechanism responsible for this observation is presently unclear. However, considering the identified major target sites of ketamine, including interactions with NMDA, non-NMDA, nicotinic cholinergic, and L-type Ca^{2+} channels (Kress, 1997), it seems worthwhile to study this effect in detail.

4.2. Induction of long-term potentiation of population EPSPs

As previously reported, tetanic stimulation in layer IV can produce long-term potentiation in layer II/III of the visual cortex of adult rats, without application of a GABA receptor antagonist (such as bicuculline) (Bear and Kirkwood, 1993). In our experiments, primed-burst stimulation in layer IV elicited long-term potentiation of the population EPSP1 and the population EPSP2 in layer II/III; however, the incidence and the extent of long-term potentiation was more in the population EPSP2 than in the population EPSP1. It seems that potentiation of each population EPSP is independent of the other because our findings showed that, in some cases, long-term potentiation occurred only in the population EPSP1 and not in the population EPSP2 and vice versa. This, in part, could be attributed to the receptors mediating the population EPSPs. Also, some slices showed long-term potentiation 30 min after train stimulation, but because of the fast decay, the extent of long-term potentiation was less than 20% 60 min after train stimulation. This type of potentiation could be called short-term potentiation, as previously reported by Castro-Alamancos and Connors (1996). However, Kirkwood et al. (1993) claimed that short-term potentiation typically was not observed in the neocortex.

As mentioned in the Introduction, there are many reports that NMDA receptor blockade inhibits long-term potentiation in the neocortex. In our experiments, ketamine decreased the occurrence and extent of long-term potentiation of the population EPSP2. Nevertheless, ketamine (100 to 200 μM) could not completely block long-term potentiation. Indeed, 50% of the slices demonstrated long-term potentiation of the population EPSP2. To examine whether the induction of long-term potentiation by primed-burst stimulation is mediated through the activation of the NMDA receptors, a selective antagonist of these receptors, AP5, was used. AP5 was unable to prevent long-term potentiation. Bear et al. (1992) reported the occurrence of long-term potentiation in the kitten visual cortex in the presence of AP5. NMDA receptor independent long-term potentiation has also been shown (Komatsu et al., 1991).

Ketamine antagonized long-term potentiation of the population EPSP1. This effect of ketamine may, in part, be attributed to its effect on EPSP1b (a component of EPSP1 mediated by NMDA receptors). Similarly, it has been reported that AP5 is also able to prevent long-term potentiation of EPSP1 (Artola and Singer, 1990). Considering that a component of the population EPSP1 (i.e., population EPSP1a) is non-NMDA receptor dependent, it seems likely that ketamine blocked non-NMDA as well as NMDA receptors, although this remains to be elucidated. Gonzales et al. (1995) demonstrated that quisqaulate-stimulated (but not kainate) responses were more sensitive to ketamine than were NMDA-stimulated responses.

We conclude that ketamine can interfere with synaptic transmission in the visual cortex. Primed-burst stimulation is an effective protocol for neocortical potentiation, and NMDA receptors are involved in the induction of long-term potentiation by primed-burst stimulation of the population EPSP1 and the population EPSP2 in adult rat visual cortex in vitro.

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