Effects of Neonatal C-Fiber Depletion on Interaction between Neocortical Short-Term and Long-Term Plasticity

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ABSTRACT

Introduction: The primary somatosensory cortex has an important role in nociceptive sensory-discriminative processing. Altered peripheral inputs produced by deafferentation or by long-term changes in levels of afferent stimulation can result in plasticity of cortex. Capsaicin-induced depletion of C-fiber afferents results in plasticity of the somatosensory system. Plasticity includes short-term and long-term changes in synaptic strength. We studied the interaction between paired-pulse facilitation, as one form of short-term plasticity, with long-term potentiation (LTP) in the neocortex of normal and C-fiber depleted freely moving rat.

Methods: Neonatally capsaicin-treated rats and their controls were allowed to mature until they reached a weight between 250 and 300g. Then animals were anesthetized with ketamine and xylazine. For recording and stimulation, twisted teflon-coated stainless steel wires were implanted into somatosensory cortex or corpus callusom. In experiments for LTP induction, after two weeks of recovery period, 30 high frequency pulse trains were delivered once per day for 12 days. Paired-pulse ratio (PPR) was monitored before and after the induction of LTP in capsaicin-treated and control rats.

Results: Paired-pulse stimulation affected all field potential components at intervals < 200 ms. The largest changes occurred at intervals between 20- 30 ms. C-fiber depletion postponed the development of LTP, whereas it had no effect on PPR.

Discussion: This finding provides further evidence that the expression of this form of LTP is postsynaptic. Furthermore, these results suggest that the effect of C-fiber depletion on cortical LTP is also postsynaptic and, therefore, is not caused by a decrease in neurotransmitter release.

1. Introduction

Neurons in the mammalian cerebral cortex are connected into networks by synapses whose strengths can change as a function of recent activity (Buhl et al., 1997; Galarreta & Hestrin, 1998; Goriounova & Mansvelder, 2012; Varela & Sen & Gibson & Abbott & Nelson, 1997). Plasticity includes short-term [e.g., paired-pulse facilitation (PPF) and paired-pulse depression (PPD)] and long-term changes in synaptic strength [e.g., long-term potentiation (LTP) and long-term depression (LTD)] (Ziakopoulos & Tillett & Brown & Bashir, 1999). LTP and LTD of synaptic transmission have been extensively studied in the rat brain and are defined as an increase and a decrease in synaptic efficacy respectively, following either high-frequency stimulation (HFS) in the case of LTP, or low-frequency

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stimulation (LFS) in the case of LTD (Bear & Malenka, 1994; Bliss & Lomo, 1973; Howland & Wang, 2008; Goriounova & Mansvelder, 2012; Hunt & Castillo 2012; Lee & Kirkwood, 2011). Both LTP and LTD are thought to be biologically plausible models for the processes engaged during memory formation and storage (Bear & Malenka, 1994; Howland & Wang, 2008; Hunt & Castillo 2012; Lamont & Weber,2012).

It is widely accepted that the facilitatory effect observed with PPF is related to presynaptic mechanisms (Manita & Suzuki & Inoue & Kudo & Miyakawa, 2007; M¨uller & Felmy & Schneggenburger, 2008; Wu & Saggau, 1994; Zucker, 1973, 1989). This phenomenon is attributed to an increase in the amount of transmitter release in response to the second stimulus, and there is strong evidence that facilitation is caused by residual Ca2+ that remains in the nerve terminal from the Ca2+ influx during a previous action potential (Debanne & Gurineau & Ghwiler & Thompson, 1996; Hess & Kuhnt & Voronin, 1987; M¨uller et al., 2008; M¨uller & Felmy & Schwaller & Schneggenburger, 2007; Zucker, 1989; Zucker & Regehr, 2002). Therefore, PPF is considered to be an example of purely presynaptic plasticity (Angela, 1999; M¨uller et al., 2007; M¨uller et al., 2008; Zucker, 1989).

The mechanisms underlying PPD are poorly understood. Although postsynaptic receptor desensitization can contribute to PPD at some specialized synapses (Otis & Zhang & Trussell, 1996; Trussell & Zhang & Raman, 1993) or under some experimental conditions, most synapses exhibit a strong presynaptic component of PPD (He, 2002; Zucker, 1989, 1999).

A possible complication in understanding LTP is that there might be an interaction between PPF and LTP (Craig & Commins, 2005; Kawashima & Izaki & Grace & Takita, 2006; Maruki & Izaki & Nomura & Yamauchi, 2001 ; Schulz & Cook & Johnston, 1994; Schulz & Cook & Johnston, 1995). The presynaptic expression of paired-pulse plasticity is often used as an analytic tool for interpreting changes in behavior of presynaptic terminals associated with long-term plasticity (Akopian & Musleh & Smith & Walsh, 2000; Wang & Kelly, 1997). Therefore, a change in PPF would provide strong evidence for presynaptic involvement in LTP (Schultz, 1994).

Capsaicin (Cap)-induced depletion of C-fiber afferents result in plasticity of the somatosensory system which is manifested as a functional alteration at different levels of the somatosensory pathway (Komaki & Esteky, 2005; Kwan & Hu & Sessle, 1996; Nussbaumer & Wall, 1985; Sheibani & Shamsizadeh & Afarinesh & Rezvani, 2010; Wall & Fitzgerald & Nussbaumer & Van der Loos & Devor, 1982). Some subclass of capsaicin-sensitive C-fibers provides a primary source for the masking inhibition that normally limits the extent of the receptive fields (RF) of cortical neurons (Calford & Tweedale, 1991). Capsaicin-induced C-fiber depletion causes expansion of excitatory RFs and alters neuronal properties in the somatosensory cortex (Nussbaumer & Wall, 1985). Consistent with these findings it has been shown that C-fiber depletion alters the balance of the excitation and inhibition and expands the RF size of rat barrel cortex cells (Farazifard & Kiani, & Esteky, 2005; Farazifard & Kiani &Noorbakhsh &Esteky, 2005). Also, it has been reported that neonatal capsaicin-induced C-fiber depletion modulates experience-dependent plasticity in the rat barrel cortex (Sheibani & Shamsizadeh & Afarinesh & Rezvani, 2010). Previously, it has been reported that C-fiber depletion using neonatal Cap treatment postponed the development of the neocortical LTP (Komaki & Esteky, 2005). The aim of the present study was to address the question of whether the change acutely induced by Cap takes place in presynaptic sites, postsynaptic sites or both. To address this question, we analyzed the paired-pulse ratio (PPR) of two responses evoked by two successive stimuli at given intervals, because any change in presynaptic sites is expected to accompany changes in PPR (Jiang et al., 2004; Manita et al., 2007; Salazar-Weber & Smith, 2011; Zucker, 1989). PPR is the ratio of the amplitude of the second response to that of the first, depends on the probability of vesicular release at the synapse, and PPR has been used as an easy measure of the release probability (Manita et al., 2007).

2. Methods

2.1. Animals

This study was based on data from 27 male Sprague-Dawley rats. Nine rats were neonatally treated with Cap, and the remainders were vehicle-treated.

Capsaicin treatment: Neonatal albino rats were treated by Cap (50 mg/kg intraperitoneal [i.p.] Sigma; dissolved in saline containing 10% Tween 80 and 10% ethyl alcohol) within 48 h of birth. Control neonates were given an equal volume of the vehicle (only the capsaicin solvent). Treatment of neonatal rats with Cap effectively destroys the majority (95%) of C-fibers (Fitzgerald, 1983; Hiura, 2000; Holzer, 1991; Kiani& Farazifard & Noorbakhsh & Esteky, 2004 Komaki & Esteky, 2005; Sheibani et al., 2010; Kwan et al., 1996; Toldi & Joo & Wolfe, 1992).

Efficacy of Cap treatment in depleting C-fibers was assessed in the current study by corneal chemosensitivity test (Krahl & Senanayake & Handforth, 2001; Sheibani et al., 2010). Corneal chemosensitivity is principally mediated by C-fibers (Holzer, 1991) and its significant reduction is used as a measure of C-fibers depletion. One drop of 1% ammonium hydroxide was applied to the right eye of adult animals and the number of times they wiped their right eye in the first 10 s after application was counted. The corneal chemosensitivity was significantly reduced in the capsaicin-treated (3.9± 0.92) compared with the vehicle-treated (13.1±1.27) (t-test, P<0.001).

2.2. Surgery

Neonatally treated rats and their controls were allowed to mature until they reached a weight between 250 and 300g. Then the animals were anesthetized with ketamine and xylazine (i.p.). The procedure for implantation of recording and stimulating electrodes was as previous experiments (Komaki & Esteky, 2005; Komaki & Shahidi & Lashgari & Haghparast & Malakouti & Noorbakhsh, 2007). In brief, for recording and stimulation, twisted Teflon-coated stainless steel wire (120 m diameter ; Advent) were implanted into somatosensory cortex [AP= -1 to -2, ML= 3.5-4 , DV=2 mm] or corpus callusom (AP= -1 to -2, ML= 2 , DV=3 mm) in the same coronal plane respectively (Paxinous & Watson, 2005) (Fig. 1). Two weeks recovery period preceded experimental testing. All experiments were done in accordance with the "Principles of laboratory animal care" (NIH publication No. 86-23, revised 1996). Rats were housed individually on a 12:12 h light/ dark cycle and tested during the light cycle.

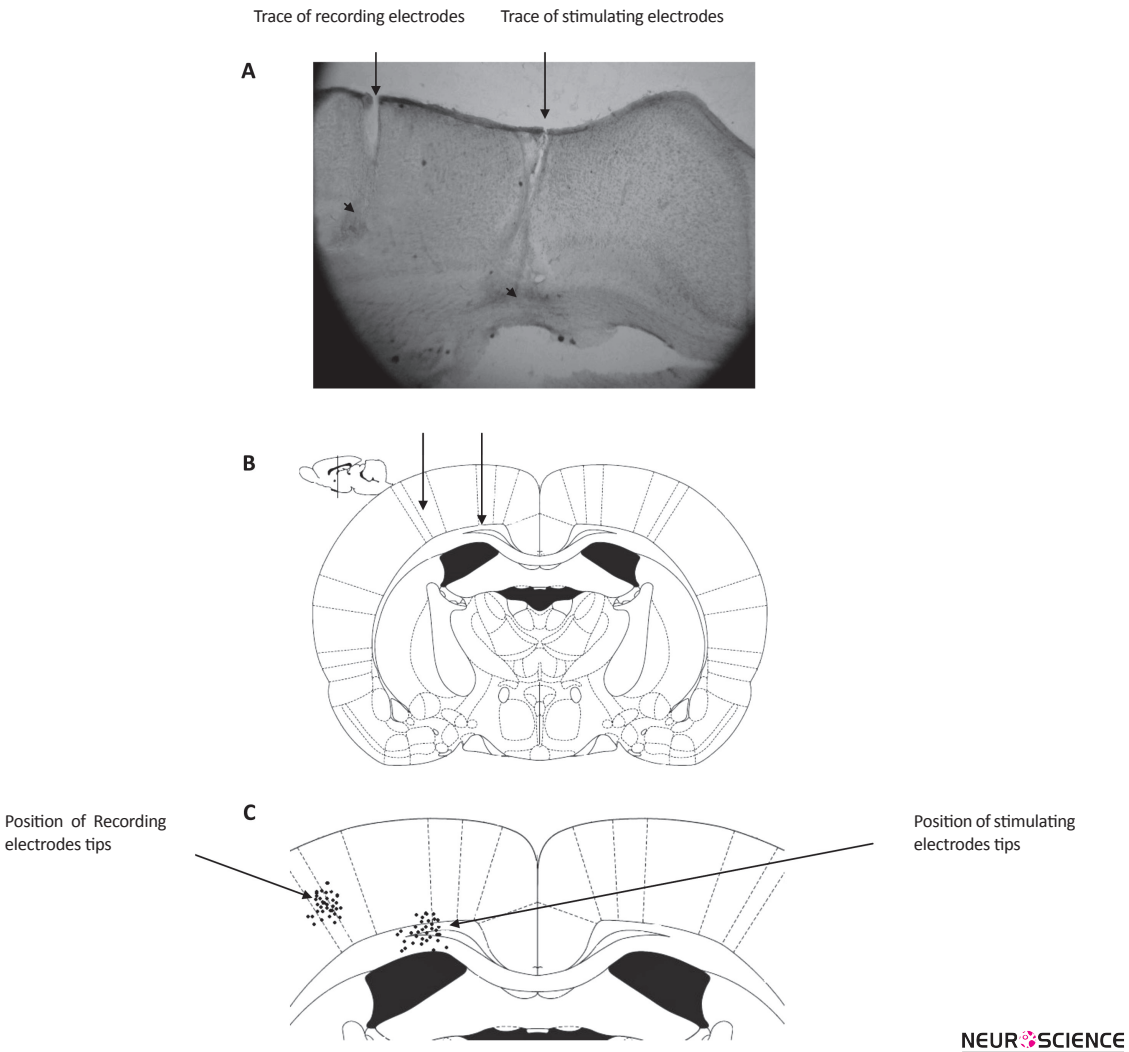

Figure 1. Histology; Electrodes placements in coronal section. A: Photomicrograph scan of a coronal section (50 µm) showing the electrodes trace. The trace of stimulating and recording electrodes can be seen at the right and left side, respectively (arrow). Arrowheads represent the place of stimulating and recording electrodes tips. B and C: Position of stimulating electrodes in corpus callosum and recording electrodes in layers V-VI of neocortical area SI are shown [adapted from Paxinos and Watson (2005)]. Scale bar represents 0.5 mm.

2.3. Input – Output Tests

Input – output (I-O) tests were similar to those described previously (Chapman, et al., 1998; Komaki & Esteky, 2005; Komaki et al., 2007; Trepel & Racine, 1998). Briefly, stimulation pulses were delivered at varying intensities to the appropriate stimulation site (see below) and the resulting cortical evoked field potentials were monitored. Single 0.1 ms biphasic square wave pulses were delivered through constant current isolation units (Pulsemaster: model A300 WPI and Isolator: model A365 WPI) at a frequency of 0.1 Hz. The I-O test included ten responses evoked at each of 10 logarithmically spaced intensities (16, 32, 64, 100, 160, 250, 500, 795, 1000, and 1260 A). The responses were filtered (0.1 Hz to 3 kHz), amplified (Differential amplifier DAM 80 WPI), digitized at 10 kHz, and stored on a computer hard drive. I-O tests were conducted every 2 days during a 1 week baseline period (Before applying HFS) and a 12 days LTP induction period.

2.4. Paired-Pulse Stimulation

Paired-pulse stimuli were used to investigate short-term plasticity (Torii & Tsumoto & Uno & Astreline & Voronin, 1997). PPS was delivered every 10 sec to the corpus callusom at 13 interpulse intervals. In every experiment, the interstimulus interval (ISI) was varied systematically from 20 ms up to 400 ms. Thus, a complete series consisted of a sequence of paired pulses with ISIs of 20, 30, 40, 50, 60, 70, 80, 120, 160, 200, 250, 300 and 400 ms. To compute PPR, the amplitude of the response to the second pulse of the pair was divided by the amplitude of the response to the first pulse in the pair. In each animal, at least three consecutive ISI series were run and averaged (Manita et al., 2007; Rozas et al., 2001).

Paired-pulse tests were conducted on the last baseline day and one day after LTP induction. Pulse intensity was set to evoke an early component at approximately 75% of the maximum amplitude (Chapman et al., 1998; Racine & Milgram, 1983).

2.5. High Frequency Stimulation for LTP Induction

In experiments for LTP induction, 30 high frequency pulse trains were delivered once per day for 12 days (Chapman et al., 1998; Komaki & Esteky, 2005; Komaki et al., 2007). Each 24 ms train consisted of 8 pulses at 300 Hz, and the trains were delivered once every 10 sec. Pulse intensity and duration were 1260 A, and 0.1 ms, respectively.

2.6. Data Analysis

The analysis of the early monosynaptic and late polysynaptic components of field potentials were similar to those described previously (Chapman et al., 1998; Komaki & Esteky, 2005; Trepel & Racine 1998). Changes in the field potentials over PPF, PPD and LTP induction and decay sessions were measured by subtracting the final baseline responses from all other baseline and potentiated responses at a single I/O intensity that best reflected potentiation or depression. The intensity that evoked a response that was approximately half the maximum amplitude was chosen for analysis. This was the sixth intensity in the I/O (250 µA) in almost all cases. The criterion for labeling a response as potentiated was that its change from the baseline average exceed that seen in any of the control responses (Racine & Teskey & Wilson & Seidlitz & Milgram, 1994; Racine & Chapman & Teskey & Milgram, 1995). Changes in response amplitudes were analyzed using mixed design ANOVAs and the Tukey post-hoc test.

2.7. Histology

Rats were deeply anesthetized with urethane (2.0 mg/kg) and perfused through the heart with formol-salin. Brain sections were cut at 50 µm and stained with tionine to verify electrode placements.

3. Results

3.1. Baseline Field Responses

In general, neocortical field potentials were similar to those described previously (Chapman et al., 1998; Komaki et al., 2007; Trepel & Racine 1998). Briefly, they appeared to have two main components: an early surface-negative response (average latency-to-peak 8.8 ms, range 7.0-11.0 ms), and a larger late response (average latency-to-peak 18.8 ms, range 17.0-25.5 ms) (Fig. 2A). (All data are reported as means ± SEM.)

Figure 2 shows neocortical field potentials evoked by paired-pulse stimulation at intervals of 20 (B), 30 (C) and 40 (D) ms, before the HFS application. Paired-pulse stimulation of the Corpus Callusom (20-400 ms ISIs) produced a facilitation of the late component to 134ms ± 10% of the control peak amplitude (Fig. 2B). PPF maximizes between 20 and 30 ms and declines as the ISIs are increased or decreased. The peak of the enhanced response occurred at a longer latency (20.8 ± 2.5 ms). Paired-pulse stimulation of the Corpus Callusom produced a depression of the early component to 20ms ± 10% of the control peak amplitude (Fig. 2B).

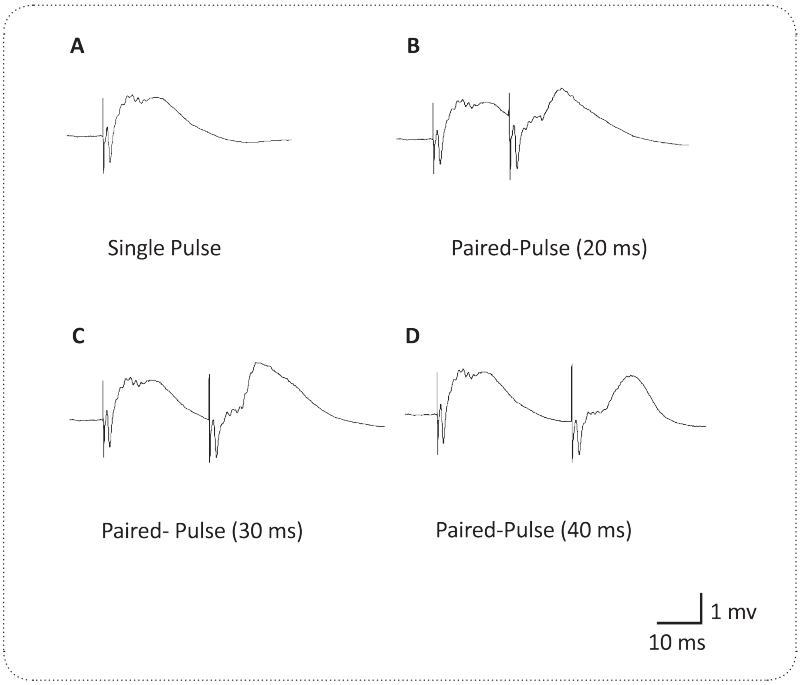

Figure 2. A representative example of filed potential evoked by paired-pulse stimulation at intervals of 20, 30 and 40 ms, before the HFS application. The stimulation intensity was 250 µA.

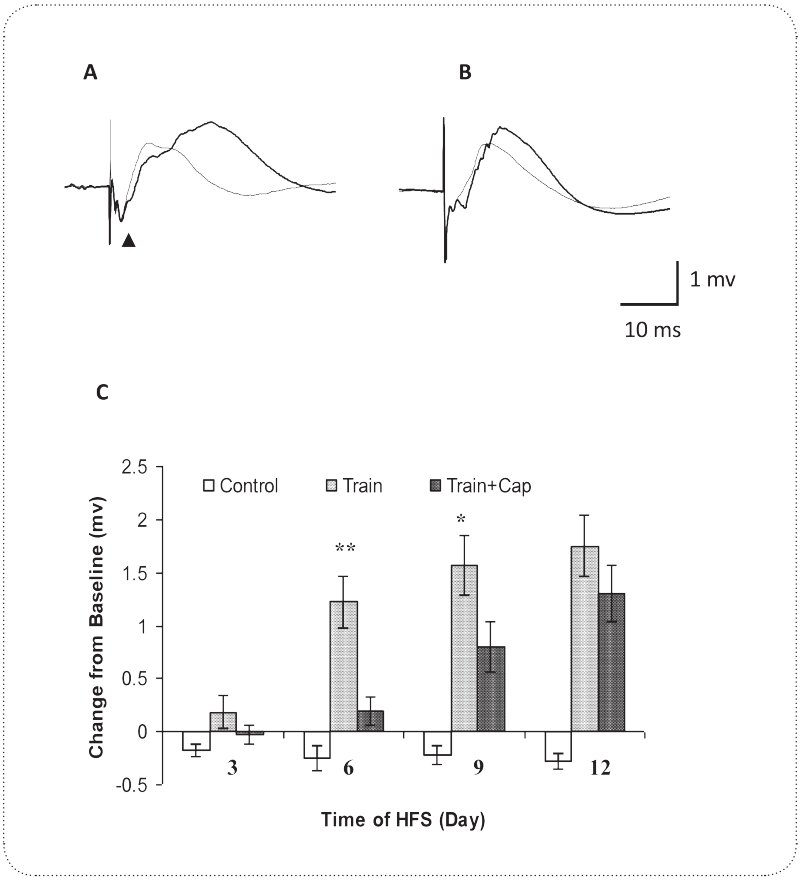

Figure 3. Potentiation effects induced by high-frequency (300 Hz) stimulation. The thin line represents an unpotentiated evoked field potential, while thick line represents an evoked field potential following 6 days of HFS in vehicle-treated (A) and Cap-treated (B) animal. This kind of stimulation caused an enhancement in the repetitive population spike (Arrowhead) activity associated with an apparent reduction in the amplitude of the early monosynaptic component and the enhancement of a longer latency polysynaptic component. The stimulation intensity was 250 µA. C: The effects of Cap on the induction of long-term potentiation in the late component of somatosensory field potential. The mean change from baseline amplitude (±SEMs) of the late polysynaptic components are shown over days. After baseline test session, the train and train + Cap groups received 12 days of high-frequency stimulation trains. Control animals did not receive HFS. Values indicate differences (mV) between the last baseline and all other sweeps for the LTP induction periods. *P < 0.05 and **P < 0.01 compare train + Cap group. High Frequency Stimulation (HFS), Capsaicin (Cap).

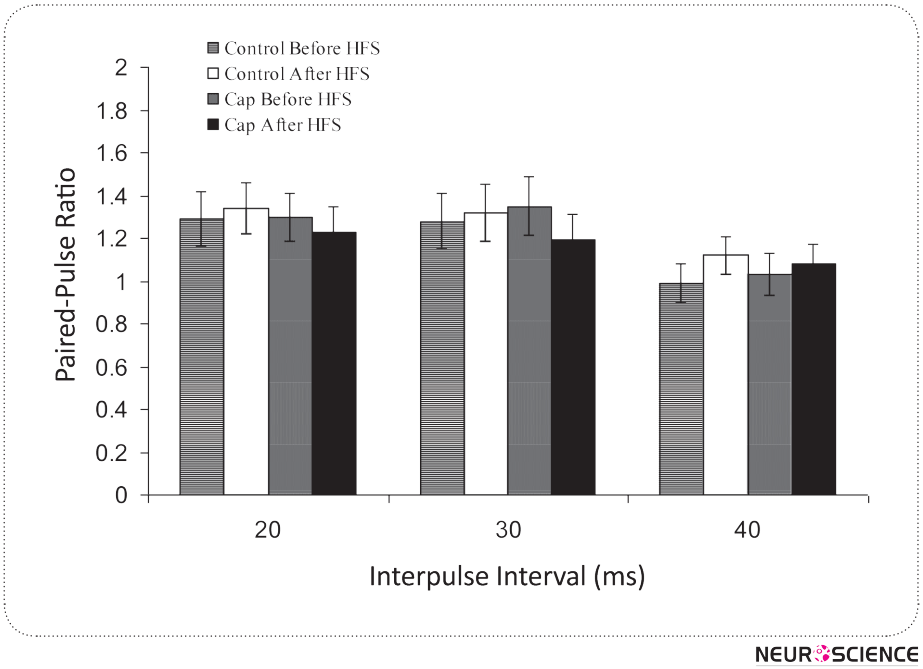

Figure 4. Paired-pulse ratio of evoked field potential was not changed by HFS. In the graph, ratios of the amplitude of the second to first field potentials evoked by paired stimulation at intervals of 20, 30 and 40 ms are plotted for all groups. Values obtained before and after the induction of LTP by 6 days of HFS. All data are expressed as means ± SEM.

High Frequency Stimulation (HFS), Capsaicin (Cap).

3.2. Effects of C-fiber Depletion on LTP Induction

Figure 3 shows representative sweeps taken from vehicle- and Cap-treated animal that received HFS for 6 days. Induction was characterized by an increase in the repetitive population spike activity which masked the enhancement of the early monosynaptic field excitatory postsynaptic potential (fEPSP) and a potentiation of longer latency polysynaptic component (Chapman, et al., 1998; Trepel & Racine, 1998). There was a significant interaction effect between session and group for late component (ANOVA; $P<0.001$), the potential magnitude of both train (n=10) and Cap (n=9) groups were significantly higher compared to the control group (n=8) at the end of the stimulation period (Tukey HSD; $P<0.005$). The train group showed significantly greater potentiation than the Cap-treated group in the 6th day of induction period ($P<0.01$).

3.3. Effects of LTP Induction on PPR of Evoked Potential

In next set of experiments, the ratios of the amplitude of the second to the first field potentials evoked by paired stimulation at intervals of 20, 30 and 40 ms are plotted for each animal (Fig. 4). Paired-pulse stimulation affected all field potential components at intervals < 200 ms. The largest changes occurred at intervals between 20- 30 ms. No significant effects of LTP induction on PPF were observed. In other words, PPR of evoked field potential was not changed by HFS ($P>0.05$). The most remarkable observation in our study was that C-fiber depletion postponed the development of LTP, whereas it had no effect on PPR.

4. Discussion

The LTP characteristics observed following HFS in our study were similar to those observed previously using 300 Hz trains (Chapman, et al., 1998; Komaki et al., 2007; Trepel & Racine, 1998). In summary, the present study has revealed that the LTP induction had no effect on PPR in our control group. Previous study has shown that C-fiber depletion using neonatal Cap treatment postponed the development of the LTP of neocortical late component. Also, it has been reported that there is no effect of C-fiber depletion on the magnitude and time course of the LTP of early components (Komaki & Esteky, 2005). Taken together, this evidence supports claims that the first component is monosynaptic and the later component is polysynaptic (Chapman, et al., 1998; Trepel & Racine, 1998). In addition, the present study has shown that C-fiber depletion using neonatal capsaicin treatment has no effect on PPR.

Findings in previous studies have provided evidence for a role of C-fibers in normal synaptic potentiation and depression in the somatosensory system which supports the notion that the selective inactivation of C-fibers can induce long-evolving shifts in the balance of inhibition and excitation in the somatosensory system (Katz & Simon & Moody & Nicolelis 1999; Komaki & Esteky, 2005). The Cap effects on cortical responses observed in previous experiments have suggested that the effect of Cap on central somatosensory responses is mainly exerted by destruction of C-fibers and not by non-specific systemic actions of Cap (Farazifard & Kiani & Noorbakhsh & Esteky 2005; Kiani et al., 2004; Komaki & Esteky, 2005). Furthermore, the selective impact of C-fiber depletion on the late evoked components suggests that this phenomenon may have a cortical origin (Chapman, et al., 1998; Komaki & Esteky, 2005 Trepel & Racine, 1998).

To explore the place of LTP in the neocortex of freely moving rat, we have examined the effects of neocortical long-term synaptic plasticity on neocortical short-term plasticity following paired-pulse stimulation. The results of our experiments strongly suggest that there is a complex interaction between the expressions of LTP. The change in PPF with LTP was obscured when viewed over all experiments because there were both significant increases and decreases in PPF in individual experiments. The magnitude and sign of the change in PPF appears to be dependent on the initial state of the synapses, and there is a significant correlation between the magnitude of LTP and the change in PPF associated with that particular amount of LTP, comparable to results from others experiments (e.g., Schulz et al., 1995). Synaptic strength is a dynamic property such that a postsynaptic potential exhibits short- and long-term changes in amplitude after different patterns of use. Long-term changes are believed to underlie learning and memory formation (Bear & Malenka, 1994: Howland & Wang, 2008; Hunt & Castillo 2012; Lamont & Weber,2012), whereas those that are shorter lasting and that occur on the time scale of seconds or less play an important role in the dynamic function of neural networks (Waldeck & Pereda & Faber, 2000). Synaptic short-term facilitation is a Ca2+ dependent elevation of transmitter release probability during repetitive stimulation of synapses that influences the information transfer between neurons (Abbott & Regehr, 2004; M¨uller et al., 2008; M¨uller et al., 2007; Zucker, 1989; Zucker & Regehr, 2002).

The second finding of this study was that C-fiber depletion had no effect on PPR. To properly understand what underlies variation in paired-pulse plasticity among synapses, as well as to use it as a tool, one would have to know what factors determine release probability and how these factors may be altered after a first stimulus (Hanse & Gustafsson, 2001; Salazar-Weber & Smith, 2011). The presynaptic expression of paired-pulse plasticity is often used as an analytic tool for interpreting changes in behavior of presynaptic terminals associated with long-term plasticity (Akopian et al., 2000; Kuhnt & Voronin, 1994; Liao & Jones & Malinow, 1992; Malinow & Tsien, 1990; Salazar-Weber & Smith, 2011; Wang & Kelly, 1997). Postsynaptic factors like the addition or removal of AMPA receptors can influence measures of short- and long-term plasticity (Lee & Kirkwood, 2011; Selig & Hjelmastad & Herron & Nicoll & Malenka, 1995). In support of this view, it has been reported that changes in the percentages of AMPA and NMDA receptors can also influence paired-pulse plasticity due to difference in their voltage dependence of activation (Akopian & Walsh, 2002; Lee & Kirkwood, 2011; Salazar-Weber & Smith, 2011). Also, it has been reported that, a change in PPF would provide strong evidence for presynaptic involvement in LTP (Schultz et al., 1994). More recent study has shown that copper significantly enhanced the PPR in the CA1 region and decreased the PPR in the CA3 region in an LTP-dependent manner. Thus, LTP caused the appearance of a copper-sensitive factor which modulated the PPR. This suggests the involvement of a presynaptic mechanism in the modulation of synaptic plasticity by copper. Inhibition of the copper-dependent changes in the PPR with cyclothiazide suggested that this may involve an interaction with the presynaptic AMPA receptors that regulate neurotransmitter release (Salazar-Weber & Smith, 2011).

The findings presented here provides further evidence that the expression of this form of LTP is postsynaptic and, therefore, is not caused by an increase in neurotransmitter release. Compared with previous studies, the novel aspect of this work is the use of a chronic preparation of freely moving animal to be able to examine the time course of PPF induction and decay and the longer-lasting cortical LTP induced by multiple stimulation sessions in the neocortex.

A major difficulty in the present study was to identify changes to individual synaptic potentials that were contained within a complex synaptic response. Since there is significant temporal overlap among the potentials, changes in one could produce apparent (but not real) changes in another. In conclusion, our findings suggest that the effect of C-fiber depletion on LTP is postsyn-

aptic and, therefore, is not caused by a decrease in neurotransmitter release.

5. Conclusion

Our finding suggests that the effects of C-fiber depletion on LTP is postsynaptic and, therefore, is not caused by a decrease in neurotransmitter release.

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