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Short-term synaptic plasticity in the rat geniculo-cortical pathway during development in vivo

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Abstract

The critical period for visual system development in rats normally peaks at postnatal three weeks and ends at postnatal five weeks. However, the change of short-term synaptic plasticity during this period has rarely been investigated. In the present study, we compared the short-term plasticity of visual cortical responses to lateral geniculate nucleus stimulation in rats at different development stages (P20, P30 and adult) in vivo. The results show that paired-pulse depression (PPD) and frequency-dependent depression of evoked field potentials (FP) are present in P20 rats and increase in magnitude with development. The time course of this maturation of synaptic depression parallels that of the visual critical period. The weak synaptic depression observed in juvenile rats may be important in enhancing excitatory neurotransmission at a time when synapses are immature; this could endow immature synapses with wide integrative capabilities. In contrast, suppressive temporal interactions could provide an important substrate for neuronal processing of visual information in the mature cortex.

Keywords: Paired-pulse depression; Frequency-dependent depression; Field potential; Visual cortex; Juvenile rat

Development of neocortical synaptic circuitry includes two steps: (1) the generation and migration of the neurons, and (2) the maturation of synaptic connections. The postnatal development of functional synaptic connections in the rat neocortex is characterized by the sequential appearance of excitatory and inhibitory synaptic potentials. During the very early postnatal period, excitatory synaptic inputs prevail, while evoked inhibitory postsynaptic potentials were not recorded before postnatal day 10 [17]. Thus, in contrast to the onset of excitatory responses in the developing visual cortex, synaptic inhibition develops relatively late and matures gradually during the late postnatal period. It has been suggested that this asynchronous development of excitatory and inhibitory synapses contributes to a period of development during which the brain is particularly sensitive to visual stimulation so that alterations in the pattern of visual inputs can permanently alter synaptic connections within the visual cortex [3]. This "critical period" appears to end when synaptic circuits reach their mature state. The visual critical period of rats normally peaks at postnatal three weeks and ends at postnatal five weeks [8].

Long-term synaptic plasticity (including LTP and LTD) during the critical period of postnatal development has been investigated extensively in the visual cortex of kittens and young rats both in vitro [2,14,15] and in vivo [10,12,13]. However, very little attention has been paid to the short-term synaptic plasticity of geniculo-cortical projections. In our previous study, we reported that two forms of short-term synaptic plasticity, paired-pulse depression and frequency-dependent depression, were prominent in the adult rat geniculo-cortical visual pathway in vivo [11]. Our results suggested that presynaptic Ca^{2+}-dependent neurotransmitter depletion and postsynaptic GABAergic inhibition are crucial for short-term synaptic depression in the geniculo-cortical pathway. In the current study, we examined and compared the short-term synaptic plasticity of the rat geniculo-cortical pathway at different ages to explore the development of synaptic plasticity.

Wistar rats of either sex, at ages 20 days (P20), 30 days (P30) and adult (>60 days) were used in this study. They

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were anaesthetized with urethane (1.2 g/kg, i.p.) and mounted in a stereotaxic apparatus. All pressure points and incised tissues were infiltrated with lidocaine. Throughout all experiments the rectal temperature was monitored and maintained at 37 ± 0.5 °C by a homeothermic blanket. Additional doses of urethane (0.1–0.2 g/kg) were administered if reflexes were observed. Small holes were drilled in the skull and the dura was removed to allow the insertion of electrodes in the brain as previously described [11]. All efforts were made to minimize animal suffering and to reduce the number of rats used, in accordance with the guidelines laid down by the National Institute of Health Guide for the Care and Use of Laboratory Animals.

A concentric bipolar stimulating electrode (FHC Inc., Bowdoinham, ME, USA) was implanted in the LGN (coordinates: 3.8 mm posterior to bregma, 3.5 mm lateral to the midline, and the depth adjusted to yield responses in the primary visual cortex with the largest amplitude and shortest latency). Adjustments of these coordinates were made for experiments in juvenile rats. The electrical stimulus was driven by computer-controlled ITC-18 data acquisition interface (Instrutech Corp., NY, USA), and an isolator was used to minimize the artifact. The stimuli consisted of paired-pulse with different intervals and train of pulses with different frequencies. The duration of biphasic pulse was 100 μs. A glass recording microelectrode (with an impedance of 2–3 MΩ while filled with saline) was placed in the primary visual cortex (coordinates: 7.0 mm posterior to bregma, 3.0–4.0 mm lateral to the midline, 800–1000 μm ventral to the dura). The depth of the electrode was adjusted to yield field potential (FP) responses with the largest amplitudes and shortest latencies to stimulation of the LGN. Before the beginning of each experiment, full input–output stimulus–response series was performed, and a stimulation intensity yielding 50–60% of the maximum FP was used for the remainder of the experiment. Evoked FPs were amplified and filtered at 0.1–3 kHz, digitized at 20 kHz, and were further analyzed offline.

Paired-pulse depression (PPD) was investigated by stimulating the LGN with two electrical pulses separated by inter-stimulus intervals of 20–1000 ms. Intervals between pairs of stimuli were at least 30 s. The PPD ratio was expressed as the size of the second FP amplitude relative to the first FP amplitude. Trains of stimuli (15 stimuli at 10, 20 and 50 Hz) were also used to explore the synaptic frequency plasticity. Intervals between trains of stimuli were at least 60 s. The depression evoked by a train of pulses is called frequency-dependent depression [9]. Unless otherwise indicated, averaged data are presented as mean ± S.E.M. Statistical significance was evaluated by *t*-test.

Following paired-pulse stimulation of the LGN, the amplitude of the second FP recorded in the primary visual cortex of the P20 rats was depressed relative to the amplitude of the first FP. Typical FPs evoked by paired stimuli separated by inter-stimulus intervals of 50, 100 and 1000 ms were shown in Fig. 1A. The PPD ratios depend on inter-stimulus interval. Fig. 1B shows the relationship between the averaged PPD ratio and inter-stimulus intervals. Normally, PPD was prominent at short inter-stimulus interval. However, a weak depression of the second FP was still detected at inter-stimulus intervals of up to 1000 ms. Most thalamic afferents to neocortex fire at frequencies ranging between 1 and 100 Hz [9] under physiological conditions, and it is impossible to predict the steady-state cortical responses from the paired-pulse responses [18]. So we used 15-pulse train stimulation at three different frequencies (10, 20 and 50 Hz) to investigate the changing trend and steady-state behavior of this synaptic trans-

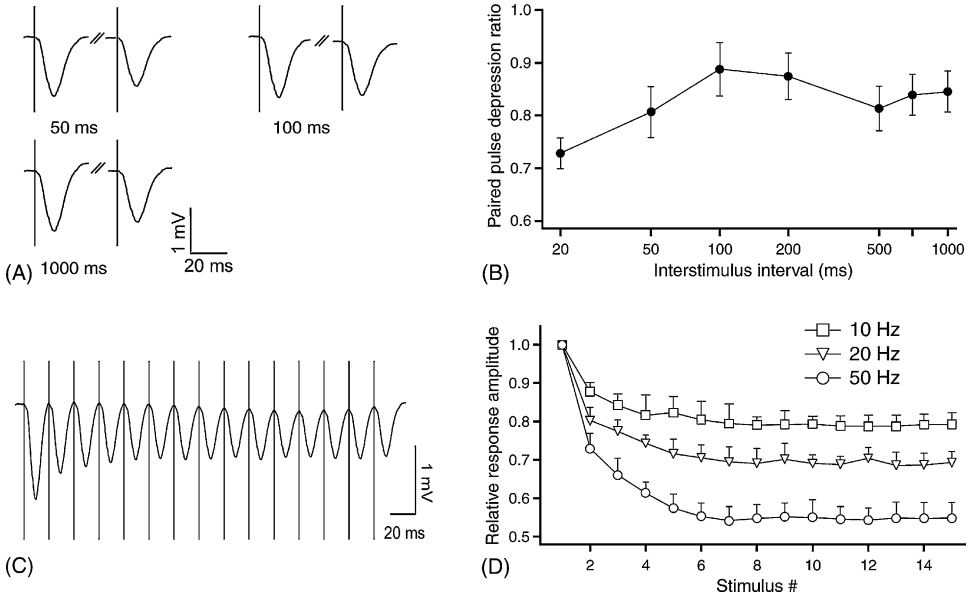

Fig. 1. Paired-pulse depression and frequency-dependent depression in the visual cortex of P20 rats. (A) An example recording showing FPs induced by pairs of LGN stimuli separated by inter-stimulus intervals of 50, 100 and 1000 ms. Long vertical lines are stimulus artifacts. (B) The averaged PPD ratio at different inter-stimulus intervals ($n = 8$). A PPD ratio was measured as the ratio between the peak amplitudes of the second and first FPs. (C) An example of FPs induced by stimulating LGN with trains of pulses at 50 Hz. Compared to the first FP of the train, the amplitude of the second and subsequent FPs decreased steeply with 50 Hz stimulation. (D) Relative response amplitude of FPs recorded at three different stimulus frequencies, indicating that the depression is dependent on the frequency of stimulus applied to the LGN ($n = 8$). Higher stimulus frequencies caused a steeper depression, i.e. smaller amplitude of steady-state responses.

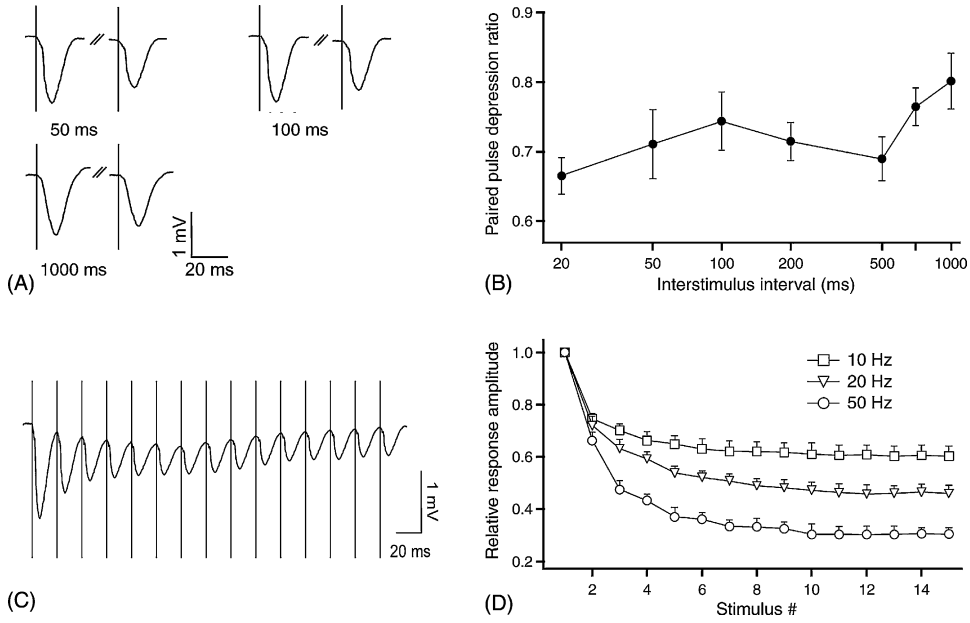

Fig. 2. Paired-pulse depression and frequency-dependent depression in the visual cortex of P30 rats. (A) An example showing FPs induced by pairs of LGN stimuli in different inter-stimulus intervals (50, 100 and 1000 ms). (B) The averaged PPD ratio at different inter-stimulus intervals ($n = 11$). (C) An typical FPs induced by stimulating LGN with 50 Hz pulses train. (D) Averaged curves of relative response amplitude of FPs evoked by 10, 20 and 50 Hz train stimulation ($n = 11$).

mission. Fig. 1C shows typical evoked cortical field potentials by 15 stimuli at 50 Hz. The amplitude of the field potential was decreased progressively by 50 Hz stimulation. The depression by repetitive stimulation is dependent on stimulation frequency (Fig. 1D). In contrast to paired-pulse effects, the steady-state depression and the decreasing speed increased monotonically across the measured range of frequencies. Higher frequency of stimulation will cause more steeply depression and less amplitude of steady-state responses. The steady-state depression ratio was expressed as the size of the last PSP amplitude relative to the first PSP amplitude. Field potential recordings in P30 rats showed even stronger short-term synaptic depression to both paired-pulse stimuli and train stimuli (Fig. 2).

Although the short-term synaptic plasticity was observed in both adult and juvenile rats, the amount of depression was apparently different. Fig. 3A compares the PPD ratios in adult and juvenile rats. The PPD ratios of P30 rats were significantly different from the PPD ratios in adults only at intervals of 20–100 ms ($p < 0.05$). In contrast, the PPD ratios of P20 rats were significantly different from the PPD ratios in adults at all intervals tested. The difference between PPD ratios observed in P20 rats and adult rats was especially prominent at interstimulus intervals of 100–500 ms ($p < 0.01$). Fig. 3B compares the frequency-dependent depression ratios recorded in adult and juvenile rats. The depression ratios of P30 rats were significantly different from the ratios in the adult only for trains applied at 20 Hz. In contrast, the frequency-dependent depression ratios of P20 rats were significantly different from the ratios in adult for trains applied at all tested frequencies.

In this study, we compared the short-term synaptic plasticity of geniculo-cortical projections in rats at different development stages (P20, P30 and adult) in vivo. We chose to record geniculo-

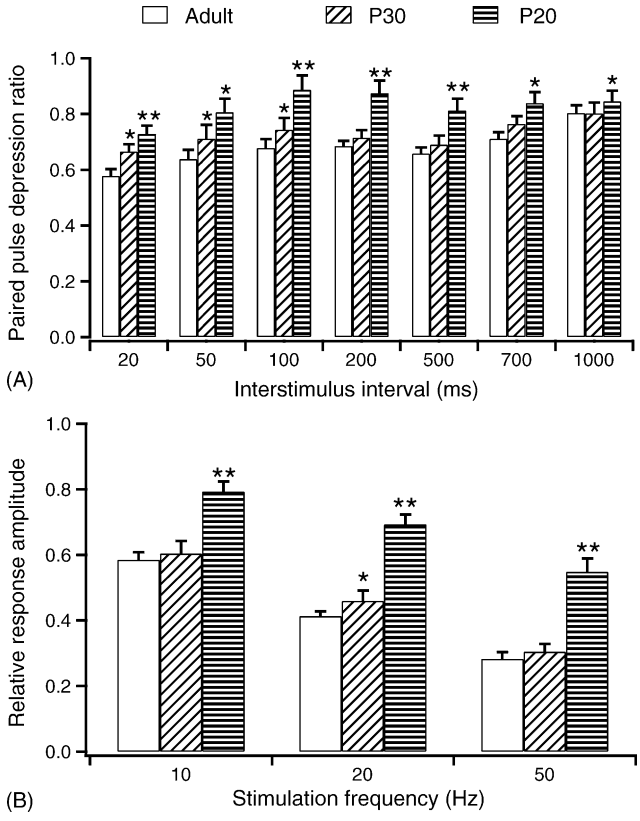

Fig. 3. Comparison of the PPD ratios (A) and frequency-dependent depression ratios (B) among rats at different ages. Compared with adult animal group by *t*-test, the ratios of P30 rats are higher only at several data points at level $p < 0.05$ (*). In contrast, the ratios of P20 rats are significantly higher at all data points recorded, and the levels are $p < 0.01$ for most points (**).

cortical responses in rats at postnatal day 20, day 30 and adults to examine the developmental changes in short-term synaptic plasticity that occur during the critical period. We found that evoked cortical FPs were depressed in response to pairs or trains of stimuli applied to the LGN as early as P20 and this depression becomes more prominent as the cortical circuitry matures.

The maturation of intracortical short-term synaptic plasticity has been studied previously in slices of the visual cortex obtained from rats during the first 47 days of postnatal life [16]. In their preparation, about 40% of the neurons in the P5–P10 rat visual cortex exhibited paired-pulse facilitation (PPF), while PPD was rarely observed. Most of the remaining neurons studied at these ages did not reveal paired-pulse interactions. PPD was more commonly observed in slices from older rats, and became prominent and more common than PPF in rats aged 31–47 postnatal days. It has been suggested that the maturation of PPD of excitatory responses is temporally correlated with the development of intracortical inhibitory circuitry, perhaps reflecting subtractive or shunting inhibition in the postsynaptic neuron as well as presynaptic inhibitory mechanisms. In the present study, the increased magnitude of synaptic depression that we observed in more mature rats supports the suggestion that inhibitory mechanisms may play an important role in the maturation of short-term synaptic plasticity of the geniculo-cortical pathway. Consistent with the proposed role of GABAergic inhibition in PPD, application of GABA receptor antagonists greatly decreased short-term synaptic depression of the same pathway in our previous study [11]. Under paired-pulse stimulation in this study, there was an interesting relationship between the PPD ratios and inter-stimulus intervals. Normally, paired-pulse with shorter interval induced stronger depression. However, at intervals from 200 to 500 ms, the depression was relatively stronger (Fig. 1B, 2B and 3A). This might be mediated by the slow GABAergic inhibition, evoked by the first stimulus in the paired-pulse. Unlike the intracortical short-term synaptic plasticity, which changed from mostly facilitation to mostly depression during the first 47 postnatal days in vitro [16], we observed synaptic depression following stimulation of the geniculo-cortical pathway in rats of all ages studied (P20, P30 and adult). A reasonable explanation of the difference in the plasticity of these two pathways is the release probability of synaptic vesicles in thalamocortical versus corticocortical terminals. The neurotransmitter release probability at thalamocortical synapses is reported to be much higher than that at intracortical synapses [4,6]. Many studies have suggested that differences in release probability could explain the pathway-specific variance in short-term synaptic plasticity [5]. Higher release probability could cause presynaptic neurotransmitter to deplete more quickly and therefore to increase the degree of short-term depression [20]. There might also be some anatomical difference that one single neuron in visual cortex of infant rat may receive more input from thalamus which in some content, also increase the release probability of thalamocortical synapse. Thus, the depletion of presynaptic transmitter may contribute to the short-term synaptic depression observed in this study.

The reduced synaptic depression that we observed in juvenile rats may be important in enhancing excitatory neurotransmission at a time when synapses are immature. This could endow immature synapses with wide integrative capabilities as suggested in motor cortex of juvenile rats [1] and could not severely weaken the competition between thalamic inputs from two eyes, which has been suggested to play an essential role in the formation of ocular dominance columns [19]. In contrast, in the mature cortex, suppressive temporal interactions could provide an important substrate for the variety of the visual response properties recorded in the visual cortex such as nonlinear temporal summation, orientation selectivity and direction selectivity [7].

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