Short-Term Synaptic Plasticity in the Visual Cortex During Development

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The maturation of short-term synaptic plasticity was studied in slices of the visual cortex obtained from rats during the first 47 days of postnatal life. Responses of cortical neurons to repetitive stimulation of the white matter at frequencies >5 Hz were examined by recording intracellularly at the resting membrane potential level. Paired-pulse facilitation, an increase in the excitatory intracellular response following an initial response, was present in ~40% of the neurons studied from postnatal day 5 (P5) to P10. Most of the remaining neurons studied at these ages did not reveal paired-pulse interactions. There was a progressive, age-related increase in the proportion of cells displaying paired-pulse depression, a decrease in the second excitatory response relative to the first, and a concomitant decrease in the proportion of cells displaying paired-pulse facilitation. Thus, at P31–P47 approximately half of the neurons revealed depression of synaptic transmission following an initial stimulus, while most of the other neurons displayed a lack of temporal interactions. At these later ages, inhibitory potentials also displayed paired-pulse interactions. Maturation of paired-pulse depression of the excitatory response is temporally correlated with the development of intracortical inhibitory mechanisms and may reflect subtractive or shunting inhibition in the postsynaptic neuron as well as presynaptic inhibitory mechanisms. Consistent with a role of GABAergic inhibition, application of GABA receptor antagonists produced reversible blockade of paired-pulse depression. In conclusion, cortical neurons display substantial maturation in short-term synaptic plasticity during the first postnatal month. Temporal facilitation may be important in enhancing excitatory neurotransmission at a time when synapses are very immature. In the mature cortex, suppressive temporal interactions could provide an important substrate for neuronal processing of visual information.

Introduction

Repetitive activation of synapses in the central nervous system is known to affect the responses to subsequent stimulation of the same pathway. This type of neuronal temporal interaction has been mainly studied in the hippocampus, where an excitatory postsynaptic response following the first response is facilitated for a wide range of frequencies (Alger and Teyler, 1976; Creager *et al.*, 1980). The mechanism underlying paired-pulse facilitation of excitatory responses is thought to involve depression of the second inhibitory potential (Davies *et al.*, 1990; Nathan and Lambert, 1991), although increased release of excitatory neurotransmitter as a consequence of calcium accumulation in the presynaptic terminal may also play a role (for a review, see Zucker, 1989).

Short-term changes in synaptic efficacy may provide an important substrate for the normal processing of neural information. Thus, short-lasting synaptic facilitation would enhance responses involving synapses that have fired recently, while other excitatory inputs to the same neuron would be less important. Paired-pulse synaptic suppression may also play a central role in neural function. For instance, it has been suggested that suppression prevents response saturation by regulating the gain of input of visual cortical neurons (Nelson, 1991). Additionally, temporal interactions may contribute to the activity-dependent formation and rearrangement of neural connections that occurs in the mammalian central nervous system during development (for a review, see Goodman and Shatz, 1993). One remarkable example of neural rearrangements is observed in the visual cortex of higher mammals: monocular deprivation of visual stimulation during a critical period of development results in a shift of ocular dominance of visual cortical neurons in favor of the open eye (Wiesel and Hubel, 1965). Similar changes have also been recently shown to occur in the rat visual cortex during the first postnatal month (Fagiolini *et al.*, 1994). By enhancing depolarization in response to repetitive, high-frequency activation of synaptic inputs, short-lasting facilitation could conceivably play an important role in synaptic plasticity during this developmental period. The enhanced synaptic depolarization would recruit *N*-methyl-D-aspartate (NMDA) receptors, which are blocked with Mg^{2+} at the resting potential and become effective only upon membrane depolarization (Mayer *et al.*, 1984; Nowak *et al.*, 1984). These receptors are thought to be involved in mechanisms of synaptic plasticity (for a review, see Constantine-Paton *et al.*, 1990), and their enhanced activation could therefore enable circuit rearrangements.

In view of the potential relevance of short-term synaptic interactions to visual processing and development, it is important to characterize temporal interactions in the developing and adult visual cortex. The present study examines the properties of short-term synaptic plasticity in the visual cortex at different developmental stages. We were especially interested in learning what temporal properties are present during the critical period of ocular dominance plasticity in the visual cortex. Since previous studies have indicated that effectiveness of excitatory synaptic transmission is not altered in somatosensory neocortex at frequencies ≤1 Hz (Deisz and Prince, 1989), we have used higher-frequency (5–100 Hz) stimulation. The results indicate that remarkable changes occur in temporal synaptic interactions displayed by rat visual cortical neurons during the first postnatal month.

Materials and Methods

Cortical slices from rats (Sprague–Dawley) ranging in age from postnatal day 5 (P5) to P47 and from ferrets (P30–P50) were prepared as described previously (McCormick and Prince, 1987). The animals were deeply anesthetized (sodium pentobarbital, 40 mg/kg, i.p.) and decapitated. A block of tissue containing the visual cortex was removed and placed in physiological saline at a temperature of 5°C. Slices were prepared as 400 μm thick coronal sections on a Vibratome (Ted Pella, model 1000) and placed in an interface-type recording chamber (Fine Science Tools), where they rested on lens paper. The boundary between the neocortex and white matter and the location of the recording and electrical

stimulation electrodes were made visible by illuminating the slice obliquely through a fiber-optic light system and observing the preparation with a low-power dissecting microscope. Slices were maintained at 32°C and continuously superfused with a solution containing (in mM): NaCl (126), KCl (2.5), $MgSO_4$ (1.2), $NaHCO_3$ (26), $NaHPO_4$ (1.25), $CaCl_2$ (2) and dextrose (10), saturated with 95% O_2, 5% CO_2 to a final pH of 7.4. Recording started ~2 h after the slices were placed in the recording chamber. Recordings were conducted from neurons located in the supragranular layers of the dorsolateral parts of the occipital poles of the hemispheres, a region that corresponds to the visually responsive cortex in the albino rat (Montero *et al.*, 1973). In ferrets, recordings were obtained from area 17, which extends around the caudal pole of the hemispheres (Law *et al.*, 1988).

Standard techniques were used to record from neocortical neurons (Connors *et al.*, 1982). Recording electrodes were pulled from 1.0 mm o.d., 0.5 mm i.d. omega dot capillary tubing. Micropipets were filled with 4 M potassium acetate or 4 M cesium acetate. Resistances were 30–60 MΩ. In additional experiments conducted to examine temporal interactions at different levels of membrane potential, whole-cell recordings were obtained using the patch-clamp technique as described previously (Blanton *et al.*, 1989; Ramoa and McCormick, 1994). Patch electrodes were pulled from borosilicate glass (World Precision Instruments) on a vertical pipet puller (Narishige) and had tip resistances of 4–8 MΩ. Electrodes were filled with one of the following two solutions: a potassium-based solution that contained (in mM) potassium gluconate (110), KCl (10), HEPES buffer (10), sodium EGTA (1), $CaCl_2$ (0.1), $MgCl_2$ (2), Na-ATP (2) and Na-GTP (0.2), and was maintained at pH 7.25; a cesium-based solution that contained cesium gluconate (120), NaCl (10), HEPES buffer (10), sodium EGTA (1) , $MgCl_2$ (2), $CaCl_2$ (0.1), Na-ATP (2) and Na-GTP (0.1), and was maintained at pH 7.25. The calculated free calcium concentration for these solutions was 0.01 μM. At the beginning of the recording session, neurons had some of their membrane properties and resting potential level characterized. All neurons recorded displayed behavior similar to that reported previously in the visual cortex of the developing rat (McCormick and Prince, 1987). Bipolar electrodes were used to deliver pairs of electrical stimuli (0.05–0.1 ms duration, 1–100 Hz; 30–500 μA in intensity) to the white matter directly below layer VI. The pairs of electrical stimuli were separated by 10–30 s intervals. To avoid excessive generation of multisynaptic potentials that would confuse interpretation of the results, the threshold level needed to generate excitatory postsynaptic potentials was first determined and electrical stimuli of low amplitude (i.e. up to ~20% higher than the threshold level, unless otherwise noted) were then used.

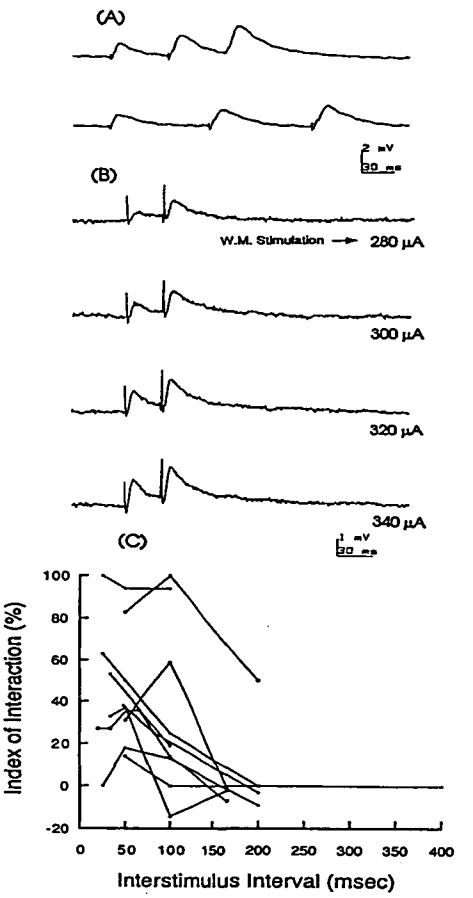

Figure 1. Examples of paired-pulse facilitation found in immature rat cortical neurons at the earliest ages studied (P5–P10). Stimulation with short interstimulus intervals caused the second and third responses to be facilitated (*A*). Facilitation was observed as an increase in peak response and was most evident at stimulus intensities near the threshold level (*B*). Plots of the index of interaction for 10 cells displaying facilitation and studied at three or more intervals show that facilitation was present mainly at brief intervals (100 ms or less).

Results

Cortical neurons in the visual cortex of the developing rat (n = 85 neurons) and ferret (n = 10) were studied by using standard and whole-cell patch-clamp recording techniques. The criteria used for selection of the visual cortical neurons studied here were similar to those previously used for selection of healthy neocortical neurons from developing and adult animals (Connors *et al.*, 1982; McCormick and Prince, 1987). Briefly, neurons were included in this study that had resting membrane potentials negative to -55 mV and could generate a train of action potentials in response to intracellular depolarizing current pulses. The primary data for these studies derive from rats. Ferrets were used to examine the general validity of observations on rats, and to examine mechanisms of paired-pulse depression (which was pronounced in ferret neurons at the ages examined).

Repetitive activation of cortical synapses at short interstimulus intervals influenced the magnitude of the second synaptic response at every age studied. However, the properties of the response to paired stimuli and trains of several stimuli applied to the underlying white matter were found to display marked changes with age. Thus, dual stimulation of white matter separated by an interval of <200 ms induced the second intracellular excitatory potential to be stronger than the first in ~40% of the neurons studied at P5–P10. Most of the remaining neurons studied at these ages did not reveal temporal interactions. Figure 1 shows examples of interactions obtained from P5 to P10 rat visual cortex. Facilitation occurred at short interstimulus intervals (Fig. 1*A*) and was clearest at low intensities (i.e. up to 20% higher than the threshold level) of white matter stimulation needed to generate excitatory postsynaptic potentials (Fig. 1*B*). An 'index of interaction' was defined as the percentage increase (in case of facilitation) or decrease (in case of depression) in the amplitude of the second response relative to the first. Plots of the index of interaction (Fig. 1*C*) for cells that displayed facilitation and were examined at three or more intervals (n = 10 cells) show the extent of facilitation at short interstimulus intervals, and the decrease in facilitation with increase in interstimulus interval.

Although paired-pulse facilitation could also be observed in older rats aged P11–P27, the proportion of cells displaying facilitation decreased with age so that after the first postnatal month, paired-pulse facilitation was rarely seen (see below). In contrast, paired-pulse depression became more common: pairs or trains of stimuli applied to the white matter at short interstimulus intervals caused the second and successive

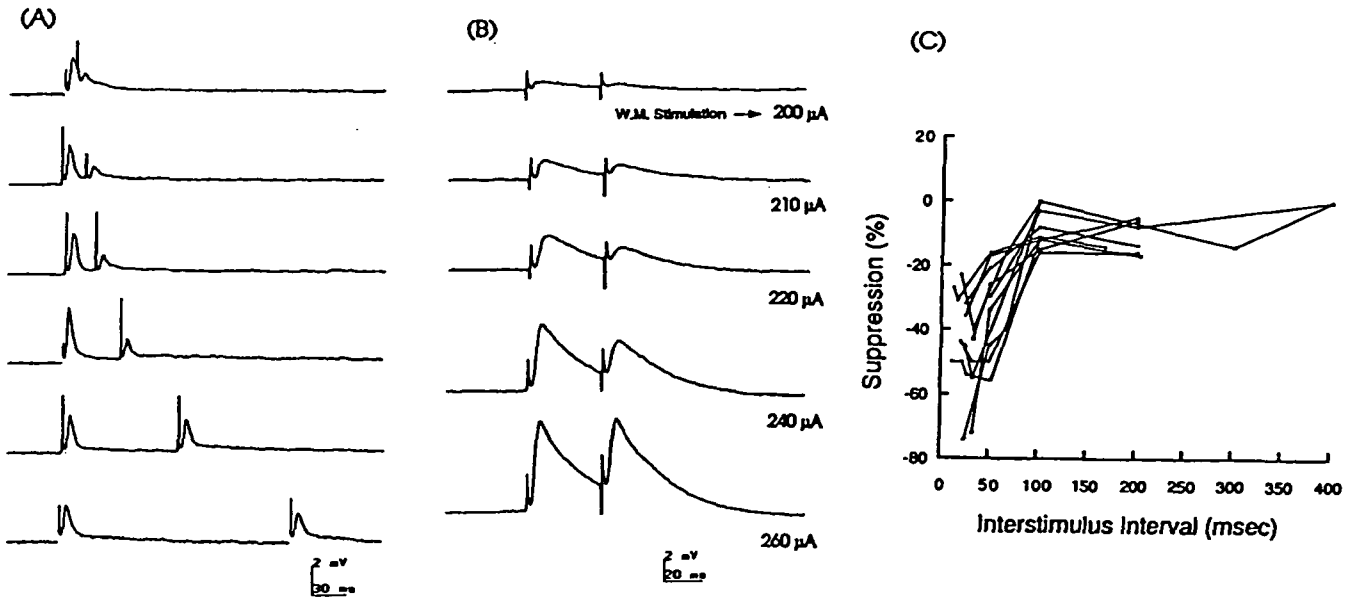

Figure 2. Examples of paired-pulse depression present in mature (P31–P47) rat cortical neurons. Paired stimulation of white matter at short interstimulus intervals (< 100 ms) caused the second response to be depressed. Paired-pulse depression was found to vary markedly according to the stimulation parameters used: it was strongest for short interstimulus intervals (*A*) and could be seen more clearly when white matter was activated using near-threshold intensity stimulation (*B*). Plots of the index of interaction for 11 mature cells showing suppression that were studied at three or more intervals show that suppression was present mainly at brief intervals (< 100 ms). Recordings at resting potential level.

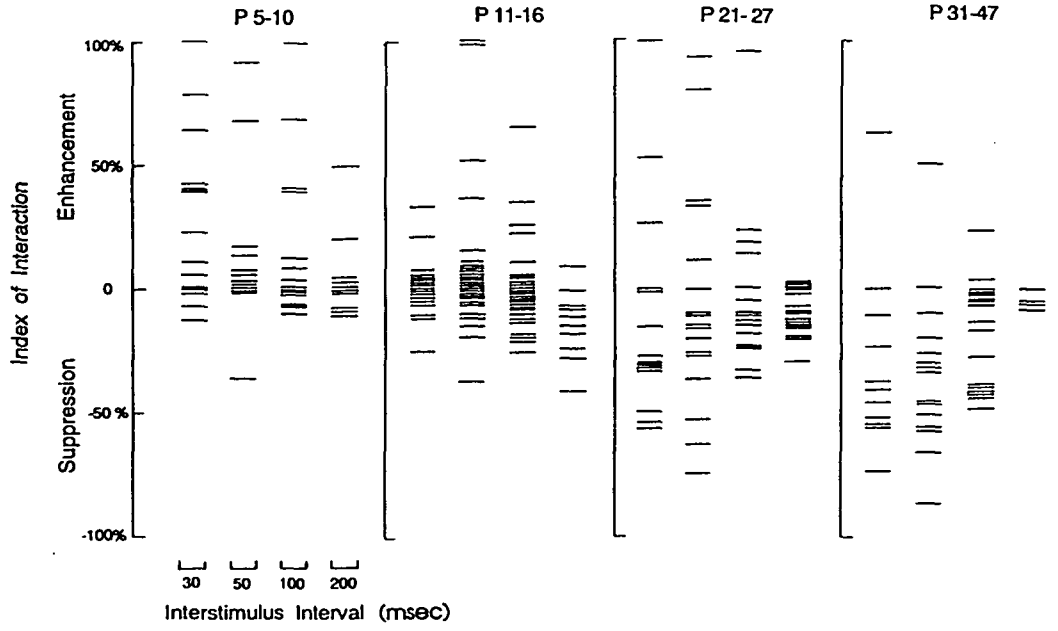

Figure 3. Index of temporal interactions (i.e. percentage increase or decrease observed in the second response relative to the first) of excitatory responses for each cell studied in rat visual cortex. The results pooled at the four different age groups reveal statistically significant ($P < 0.01$, Wilcoxon's test of results at P5–P10 and P31–P47) age-related changes in the characteristics of temporal interactions. The columns show the index for different interstimulus intervals.

synaptic responses to be depressed relative to the first in approximately half of the cells studied at P31–P47. Similar paired-pulse depression was also observed in several of the neurons studied in the ferret visual cortex. Examples of recordings from rats are shown in Figure 2 and illustrate the strong temporal interactions present in the older animals. The dependence of these interactions on interstimulus interval is evident: the magnitude of the depression was found to decrease with longer interstimulus interval duration (Fig. 2*A*). Plots of the index of interaction for cells ($n = 11$) that displayed suppression and were examined at three or more intervals show the extent of suppression at short interstimulus intervals, and the decrease in

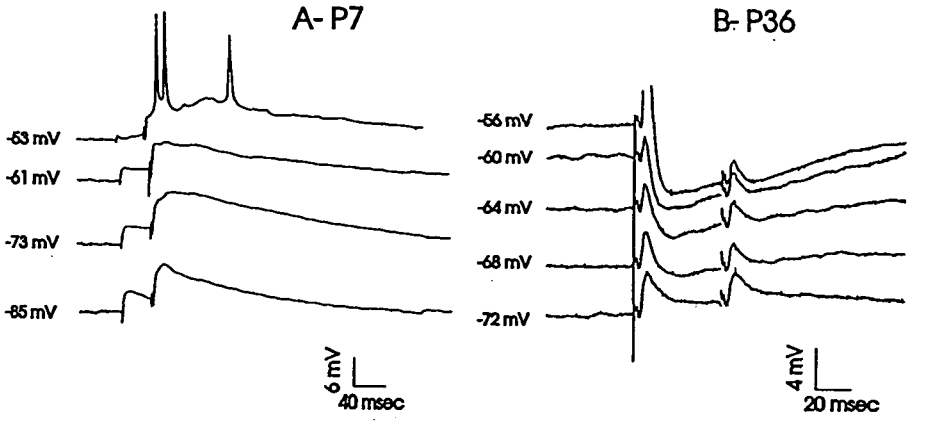

Figure 4. Temporal interactions at different levels of membrane potential were examined by using patch-clamp techniques. Paired-pulse facilitation of the excitatory post-synaptic response in a P7 rat was observed at both hyperpolarized and depolarized membrane potentials (*A*). Paired-pulse depression in an older neuron was also present at different membrane potentials (*B*). In the older cell, the second excitatory response is superimposed on an inhibitory postsynaptic potential with reversal potential of ~ −68 mV.

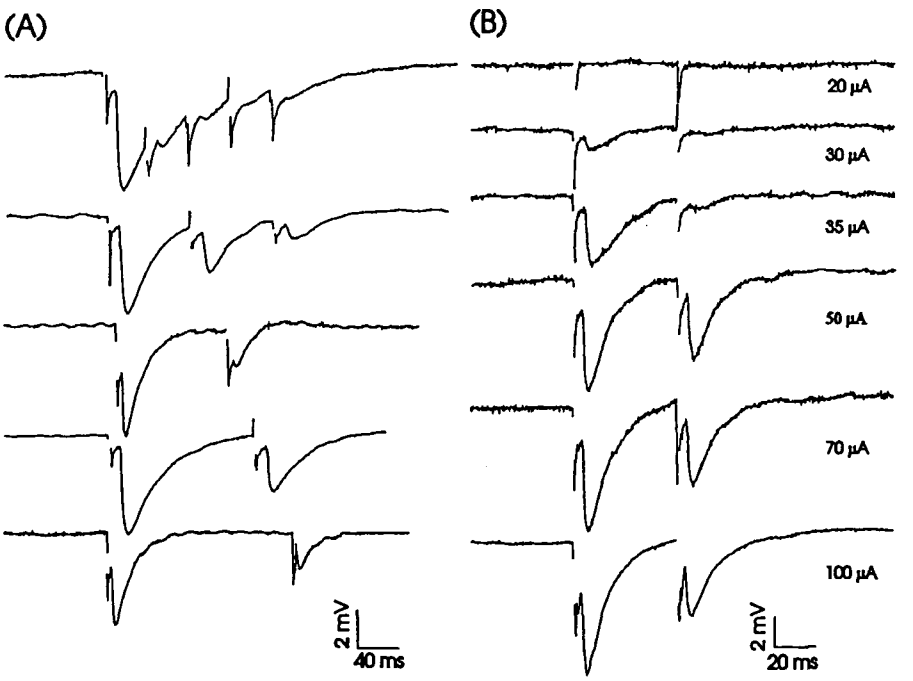

Figure 5. Temporal interactions of inhibitory potentials were characterized by depolarizing the neuron to ~ −15 mV by using patch-clamp techniques. Robust paired-pulse depression of inhibitory potentials in a P36 ferret cortical neuron was observed for a large range of stimulus frequencies (*A*) and intensities (*B*).

suppression with increase in interstimulus interval (Fig. 2*C*). Amplitude of white matter stimulation was also a major factor influencing temporal interactions in visual cortex. Depression was stronger near threshold levels and could become less evident or even disappear when high-amplitude stimuli were applied (Fig. 2*B*). In view of the dependence of temporal interactions on stimulation parameters, the stimulus intensities used in additional tests were only 10-20% higher than the threshold levels, unless otherwise noted.

To quantify the developmental changes in temporal interactions of synaptic responses, the index of interaction was calculated for each cell studied in the rat cortex. The results pooled at four different age groups using four interstimulus intervals are shown in Figure 3. Paired-pulse facilitation, common at P5-P10, was rarely observed in the more mature P31-P47 neocortex. In contrast, there was a progressive increase with age in the proportion of cells displaying depression of the second response: paired-pulse suppression was rarely present during the first 10 postnatal days, but was present in over half of the neurons after the first postnatal month. The differences in the index of interaction between P5-P10 and P31-P47 were significant [$P < 0.01$, Wilcoxon test (see Snedecor and Cochran, 1989)].

The maturation of temporal synaptic interactions described here correlates in time with the reported maturation of GABAergic inhibition in the rat neocortex (Luhmann and Prince,

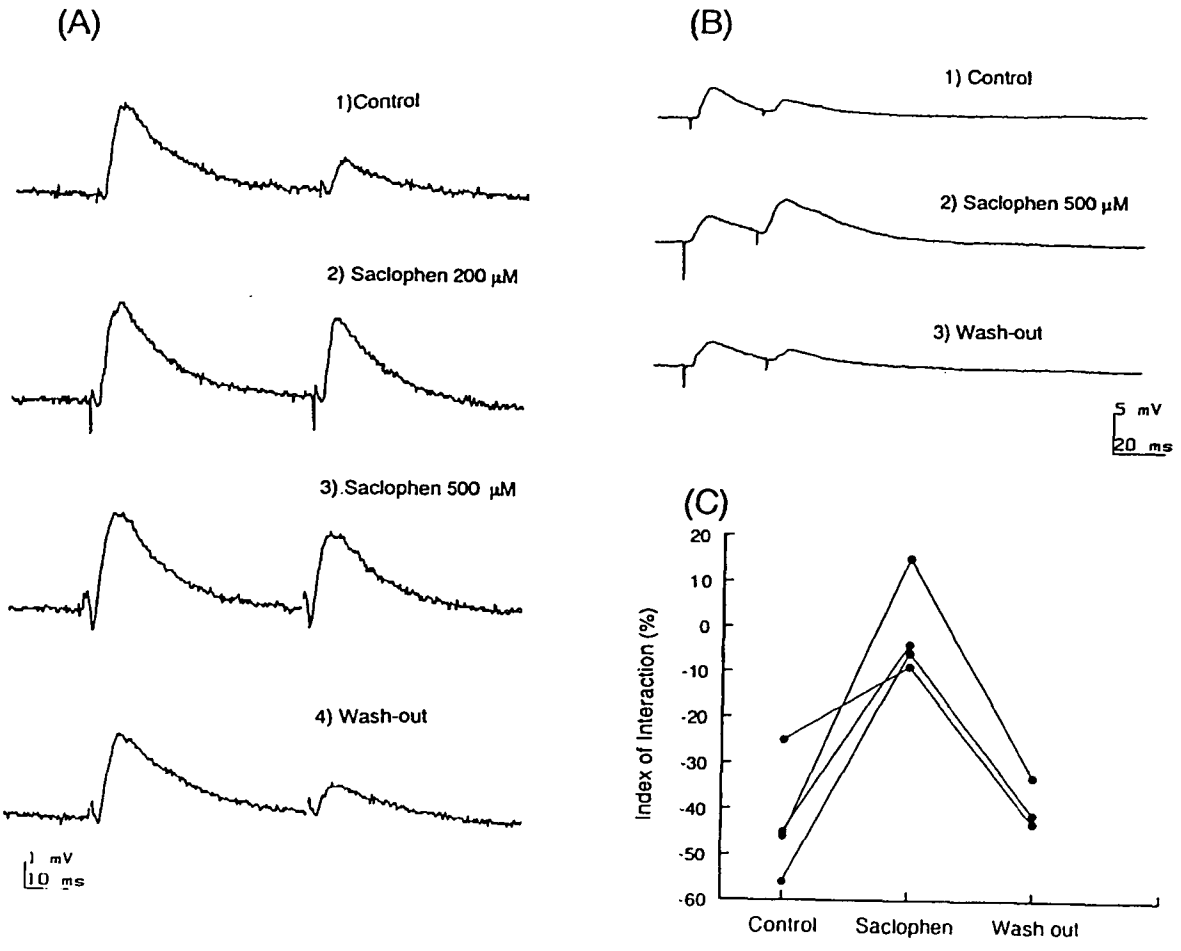

Figure 6. The mechanisms that contribute to paired-pulse depression were examined by administration of the $GABA_B$ antagonist 2-hydroxy-saclofen via the perfusion fluid. Intracellular recordings from two rat neurons (*A* and *B*) illustrate that saclofen blocked partially and reversibly the synaptic depression. In one case (*B*), application of saclofen revealed synaptic facilitation which was probably masked by the inhibitory input. The results from the four rat cells studied with saclofen have been pooled together in (*C*). Recordings were conducted at resting potential level.

1991). It is conceivable, therefore, that mature inhibitory processes are required for the paired-pulse depression seen in older neurons. Our observations are consistent with this possibility. Paired-pulse facilitation was present in immature neurons studied at membrane potentials varying from -85 to -55 mV (n = 5 cells), as shown in the recordings of Fig. 4*A*, obtained from a P7 rat neuron. Paired-pulse facilitation in this immature cortical neuron was sufficiently strong that it contributed to evoke action potentials, seen superimposed on the second excitatory response (Fig. 4*A*). Older neurons displayed paired-pulse synaptic depression at different membrane potentials (n = 6 cells), as shown in the recording of Fig. 4*B*. A pronounced inhibitory postsynaptic response with a reversal potential of --68 mV followed the first excitatory response. The second excitatory response was weaker when it overlapped this inhibitory post-synaptic potential, suggesting that inhibition plays a role in paired-pulse depression.

Another result shown in Figure 4 is that the second stimulus elicited a much weaker inhibitory potential than the first. To characterize further the effect of repetitive stimulation on inhibitory responses of visual cortical neurons, inhibitory responses to paired-pulse stimulation were examined in additional cells. In these experiments, only the inhibitory $GABA_A$ receptor-mediated responses were examined by using cesium-based recording solutions (see Materials and Methods) to block $GABA_B$ receptors. Use of this solution also enabled direct examination of inhibitory responses by allowing depolarization of the neuronal membrane to 0 to -15 mV, thus decreasing the amplitude of the excitatory response. Paired-pulse stimulation of the white matter revealed that the second inhibitory potential was altered relative to the first (n = 5 cells), as illustrated in the recordings of Figure 5. In this example, robust depression was observed for a large range of stimulus frequencies (*A*) and intensities (*B*) that varied from near threshold up to at least 330% of threshold level, the highest intensity examined. Depression of the second inhibitory potential did not appear to vary markedly with stimulus strength or interval within the range tested here. In conclusion, temporal interactions also affect inhibitory responses substantially, and this may have further effects on excitatory responses to repetitive stimulation.

To examine the mechanisms that contribute to paired-pulse depression of excitatory responses, antagonists of GABA receptors were administered via the perfusion fluid. Intracellular recordings in P31-P47 rat neocortex (n = 4 cells) revealed that synaptic depression was partially and reversibly blocked by the $GABA_B$ antagonist 2-hydroxy-saclofen (Fig. 6*A*,*B*). Interestingly,

application of saclofen revealed paired-pulse potentiation in one cell (Fig. 6*B*).

Discussion

Repetitive electrical stimulation of the cortical white matter was found to induce short-term changes in synaptic transmission in the visual cortex of the rat and ferret. However, markedly different temporal interactions were observed at early and late developmental stages. Paired-pulse stimulation applied during the first 2 weeks of postnatal life induced facilitation of the second excitatory response in a large proportion of cortical neurons. Paired-pulse depression was absent at these ages, but gradually matured during the subsequent few weeks. Thus, at P31–P47, approximately half of the neurons studied revealed depression of the second excitatory response relative to the first, while very few neurons displayed facilitation. The predominance of paired pulse depression in the more mature animals is consistent with previous reports showing paired pulse depression of excitatory potentials in other cortical areas (Thomson and West, 1993; Thomson *et al.*, 1993a,b). Additionally, investigation of inhibitory responses revealed frequency-dependent suppression of inhibition similar to that reported in the rat sensorimotor cortex (Deisz and Prince, 1989) and in the hippocampus (Nathan and Lambert, 1991). In short, visual cortical neurons display marked short-term synaptic plasticity that matures during the first postnatal month in rats.

Paired-Pulse Interactions and Cortical Development

Temporal interactions may be a crucial substrate for visual system function in the adult, as in the postulated regulation of gain of input of visual cortical neurons (Nelson, 1991), and may also contribute to regulating the initial establishment and remodeling of visual cortical connections during development. In thinking about the possible roles played by paired-pulse facilitation and suppression during visual cortical development, it is useful to examine the time course of changes in these temporal interactions in relation to other developmental events known to occur within the visual cortex. During the first few days of postnatal life, a reduced number of synapses is present in cortex and these appear to be immature, containing few synaptic vesicles in the presynaptic structure (Blue and Parnavelas, 83a). During this period, paired-pulse facilitation is the predominant mode of temporal interaction in the visual cortex. Paired-pulse facilitation may, under these conditions, enable weak synaptic input to drive target neurons. Furthermore, enhancement of neuronal depolarization mediated by temporal interactions may lead to recruitment of cortical NMDA receptors (Pennartz *et al.*, 1991), which are thought to be involved in synaptic plasticity in cortex (Bear *et al.*, 1987; Constantine-Paton *et al.*, 1990). It remains to be determined whether short-term temporal interactions play a role in some types of visual plasticity, such as ocular dominance plasticity during development (Wiesel and Hubel, 1965). The sensitive period of ocular dominance plasticity in the rat (Fagiolini *et al.*, 1994) correlates with loss of facilitation and maturation of paired-pulse suppression in visual cortex, a finding consistent with the idea that functional inhibitory processes are required in visual cortical plasticity (Ramoa *et al.*, 1988; Kirkwood and Bear, 1994).

Paired-Pulse Depression and Development of Inhibition

The time course of appearance and maturation of paired-pulse depression shows strong correlation with a marked increase in the number of cortical synapses (Blue and Parnavelas, 1983b) as well as with the appearance and maturation of the GABAergic system in rat neocortex (Luhmann and Prince, 1991). Thus, inhibitory potentials were found to be rarely evoked in most immature rat cortical neurons during the first week of postnatal life (Luhmann and Prince, 1991), a time when we also rarely observed paired-pulse depression in rat cortical cells. Moreover, the efficacy of the GABAergic system in rat neocortex increases substantially during the subsequent few weeks (Luhmann and Prince, 1991), in parallel with the maturation of paired-pulse depression. This correlation suggests that inhibitory GABAergic mechanisms may underlie paired-pulse depression.

Both pre- and postsynaptic mechanisms could be evoked during paired-pulse depression. It is likely that presynaptic inhibitory mechanisms involving GABAergic receptors play a role: in the mature brain, activation of $GABA_B$ receptors has been shown to inhibit the release of neurotransmitter from presynaptic terminals (Bowery *et al.*, 1980). Recurrent presynaptic inhibition on afferents to cortical cells via $GABA_B$ receptors is implicated by the observation that blocking $GABA_B$ receptors with saclofen prevents paired pulse depression (Fig. 6*A*) and might even unmask paired-pulse facilitation (Fig. 6*B*). Alternatively, subtractive or shunting inhibition in the postsynaptic neuron can lead to depression of the second postsynaptic response.

The mechanisms mediating paired-pulse depression are likely to be complex. In the hippocampus, presynaptic inhibition is thought to lead mainly to paired-pulse facilitation by decreasing the release of GABA into the synaptic cleft, thereby facilitating the second excitatory response (Davies *et al.*, 1990; Nathan and Lambert, 1991; Davies and Collingridge, 1993). If this also occurs in the cortex, this mechanism could explain the paired-pulse depression of inhibitory potentials shown here and in another recent study of the visual cortex (Nelson *et al.*, 1996). However, it is unlikely that presynaptic inhibition leading to decreased release of GABA would be involved in paired-pulse depression of excitatory responses in cortical neurons. Another possibility is that presynaptic glutamate receptors play a role: they have been suggested to participate in paired-pulse depression by decreasing excitatory monosynaptic transmission (Forsythe and Clements, 1990). Finally, it is possible that desensitization of excitatory amino acid receptors in visual cortex is also involved (Hestrin, 1992).

Paired-Pulse Interactions and the Time Scales of Cortical Plasticity

There is considerable evidence that long-lasting changes in synaptic strength, namely long-term potentiation (LTP) and long-term depression (LTD), can be induced in the visual cortex by appropriate stimulation paradigms (Kirkwood *et al.*, 1993). The mechanisms underlying LTP and LTD are subjects of intense study (Bear and Malenka, 1994). It is likely that plasticity of cortical synapses occurs over a range of time scales, with near-instantaneous cortical dynamics (based on interactions between different kinds of synaptic currents, membrane currents and membrane properties) at one extreme, and LTP and LTD at the other. Paired-pulse interactions constitute synaptic plasticity at the short end of the time scales. Each kind of plasticity probably involves a particular set of mechanisms. How these mechanisms relate to each other is a question of great interest for understanding cortical development and function, for it holds the promise of providing a unifying view at the

synaptic level of the link between development, activity-dependent plasticity and information processing in the cortex.

Notes

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