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Stereotypical Changes in the Pattern and Duration of Long-Term Potentiation Expressed at Postnatal Days 11 and 15 in the Rat Hippocampus

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SUMMARY AND CONCLUSIONS

1. Extracellular recordings from hippocampal area CA1 lasting 2–8 h posttetanus were used to evaluate the duration of long-term potentiation (LTP) at two key developmental ages.

2. At day 11 LTP consistently endured for ~1 h before declining to baseline by 2.5 h posttetanus. The response could then be repotentiated, and in some cases, the repotentiation lasted longer than the original potentiation.

3. At day 15 two patterns of potentiation were observed. The first pattern was similar to that observed at day 11 in that the potentiation did not persist; however, it did endure for ~2–2.5 h before declining to baseline by 4 h posttetanus. In the second pattern the potentiation persisted indefinitely; these responses were monitored for 6–8 h posttetanus.

4. These patterns are similar to the temporal phases of LTP that have been revealed in adult rat hippocampus through pharmacological manipulations. They may reflect developmental changes during which the different cellular mechanisms underlying LTP become sequentially activated.

5. These findings are important for several reasons. First, because the different temporal phases of LTP seem to be added stepwise during development, animals of different ages could be used explicitly to elucidate the underlying cellular mechanisms of these phases in LTP. Second, because LTP is a candidate mechanism for some forms of learning and memory, these results have implications for sequential steps in the ontogeny of learning and memory. Finally, because studies of LTP have used animals of widely varying ages, including these two ages, it is important to consider whether differences in the developmental properties of LTP could influence experimental observations.

INTRODUCTION

Long-term potentiation (LTP) is a phenomenon in which synaptic transmission is enhanced for hours, days, or weeks after tetanic stimulation (Baudry and Davis 1991; Bliss and Gardner 1973; Bliss and Lomo 1973). It is widely considered to be a model for the processes underlying learning and memory and significant research effort has focused on elucidating its underlying cellular mechanisms (Madison et al. 1991). Recently, quantal analysis has been used to determine whether pre- and/or postsynaptic mechanisms mediate LTP. For these studies, animals (rats and guinea pigs) ranging in age from 10 days to fully mature adults have been used (Bekkers and Stevens 1990; Foster and McNaughton 1991; Goldman et al. 1990; Kullman and Nicoll 1992; Liao et al. 1992; Malinow 1991; Malinow and Tsien 1990; Manabe et al. 1992; Muller and Lynch 1990; Voronin et al. 1992). Although there has been considerable controversy regarding specific details in the quantal analyses, a consensus is emerging that both pre- and postsynaptic mechanisms may be involved, depending on the state of the synapses before potentiation (Bliss and Collingridge 1993; Kullman and Nicoll 1992; Larkman et al. 1992). Relatively little is known, however, about the effect that the differences in age may have on LTP.

The few studies that have focused on the ontogeny of LTP have shown an increase in magnitude and duration with age. Before postnatal day 5 in the rat, only a brief posttetanic potentiation lasting <1 min occurs; and LTP persisting >1 h does not occur before day 10 (Bekenstein and Lothman 1991b; Harris and Teyler 1984; Muller et al. 1989). There is some evidence that by day 15 the duration of LTP is approaching adult-like values, but the magnitude may be greater (Bekenstein and Lothman 1991b; Harris and Teyler 1984). In the present studies, we evaluated the expression of LTP in hippocampal slices from 11- and 15-day-old rats. These ages were chosen because they are intermediate between younger ages when only posttetanic potentiation or short-term potentiation (STP) occurs and mature ages when LTP lasts for days to weeks. In addition, these ages overlap the youngest ages that have been used for quantal analysis of LTP.

Two important differences in the present study from earlier studies of the ontogeny of LTP were measurement of the field excitatory postsynaptic potential (EPSP) and monitoring of the potentiation for several hours posttetanus. First, in the older ontogenic studies, the amplitude of the population spike was used as a measure of the synaptic potentiation. A dissociation is now known to occur between potentiation of the population spike and potentiation of the field EPSP (Andersen et al. 1980; Sekino et al. 1991; Taube and Schwartzkroin 1988). Potentiation of the field EPSP is considered a better measure of synaptic potentiation and thus it is the preferred measure for LTP. Second, in the older studies on the ontogeny of LTP, the potentiation was not routinely monitored for >1 h posttetanus. Distinct temporal phases in LTP, some of which begin ≥1 h posttetanus, have been recently discovered in the mature hippocampus (for a review see Bliss and Collingridge 1993). Considerable evidence has also accumulated to suggest that these different temporal phases of LTP have different cellular mechanisms (Davies et al. 1989; Matthies 1991). Thus, in the present study, extracellular recordings

were utilized to monitor the duration of LTP for >1 h posttetanus. Overall, our results suggest that for CA1 neurons there are profound developmental shifts in the expression of LTP between postnatal days 11 and 15.

METHODS

Transverse hippocampal slices were prepared as previously described (Harris and Teyler 1984). Long Evans rat pups (Charles River) at postnatal day 11 (range = day 11, 10:30 AM to day 12, 12:50 PM) and at postnatal day 15 (range = day 15 at 12:02 PM to day 16 at 10:30 PM) were killed by decapitation, and one hippocampus was rapidly dissected and sliced at 400-μm thickness. All of the litters had been culled to 10 at birth (day 0) to prevent "runts." The slices were maintained in vitro for ≥1 h at 32°C on netting at the interface of the bath solution and an atmosphere of humidified 95% O_2-5% CO_2 before starting each experiment. The bath solution consisted of (in mM) 117 NaCl, 5.3 KCl, 1.6 $MgCl_2$, 1.8 $CaCl_2$, 1.0 NaH_2PO_4, 26 $NaHCO_3$, and 10 glucose, pH 7.2. Extracellular field potentials were recorded from the stratum radiatum of area CA1 with glass microelectrodes (~20-μm tip) filled with 2 M NaCl. A concentric bipolar electrode (Fredrick Haer) was placed in the middle of stratum radiatum and was used to deliver 100-μs constant current stimuli. The extracellular EPSP was digitized at 10.2 kHz on a Dell model 220 computer using an RC Electronics A-D board and running "Scope" software (gift from T. Dunwiddie and G. Rose). The maximal initial slope and peak amplitude of the EPSP was measured for each event. The observed physiology was not dependent on whether the slope or peak amplitude was measured. Pulse sequences were generated on a Master 8 pulse generator (AMPI) that triggered a stimulus isolation unit (WPI).

After the stimulating and recording electrodes were positioned, a stable response was monitored for ≥5 min (or the slice was not used), then increasing stimulus intensities were applied until a maximal response was obtained. The response was then monitored at the stimulus intensity that produced the half-maximal response. All of these stimuli were given at one per 30 s and the total pretetanus recording time lasted from 25 to 102 min, depending on the experiment. Tetanus was delivered at the stimulus intensity producing the half-maximal response and consisted of two trains of 100 stimuli at 100 Hz, 20 s apart. Posttetanus responses were initially monitored at one per 30 s followed by prolonged periods of response monitoring at stimulus frequencies including 1 per 30 s, 1 per 5 min, or 10 stimuli at 0.1 Hz delivered once every 10 min. The observed physiology was not dependent on differences in the total incubation times, the length of the pretetanus monitor or the rate of stimulation during the posttetanus monitor. Responses are reported as percent increase in EPSP slope over control, which was the average slope over the last 10 min of the pretetanus monitor. In all figures, the last 10 min of the pretetanus monitor are displayed, and the times are reported as minutes or hours posttetanus.

RESULTS

LTP induction and sensitivity to N-methyl-D-aspartate antagonists at days 11 and 15

At day 11, 22 slices from 16 different animals were tested for LTP. Eleven slices from 11 different animals showed LTP. Of the other 11 slices, 6 were unstable or unresponsive and no tetanus was delivered, whereas 5 had good physiological responsivity, yet tetanus failed to induce LTP. At day 15, 14 slices from 10 different animals were tested for LTP. Eleven of these slices from eight different animals showed LTP and three failed to show potentiation after the tetanus.

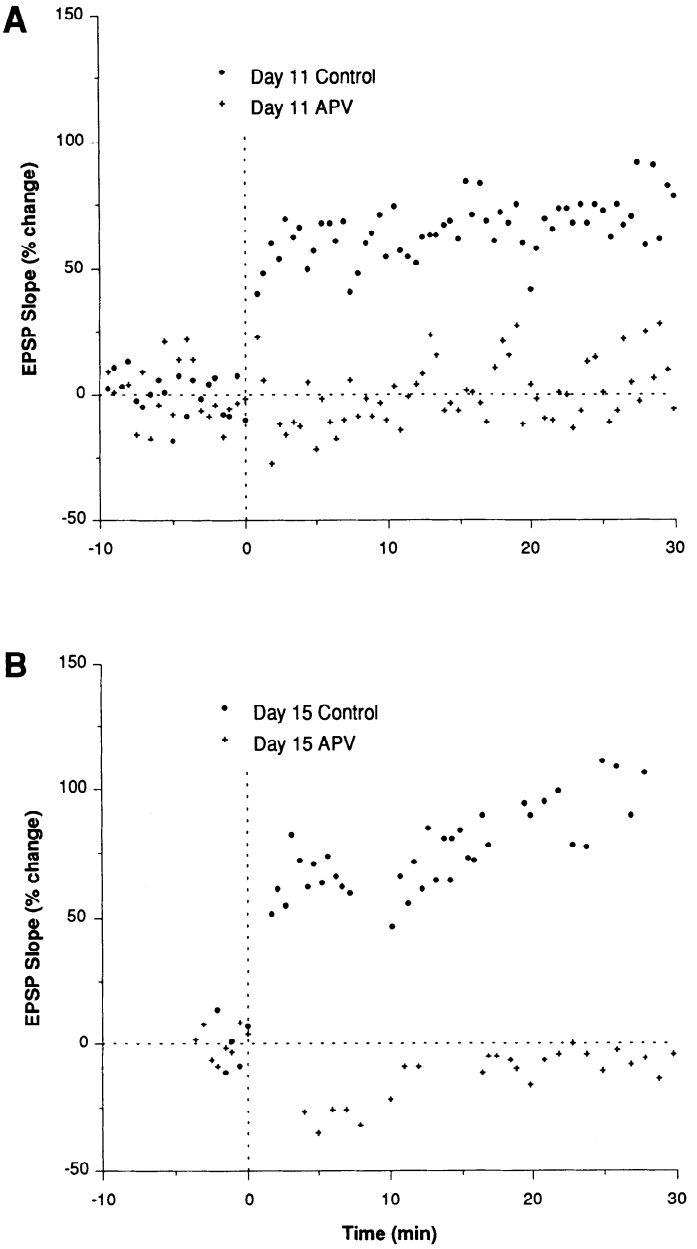

FIG. 1. Long-term potentiation (LTP) in area CA1 is 2-amino-5-phosphonovaleric acid (APV) sensitive at both ages. Slices were bathed in either normal media or media containing 50 μM APV to block *N*-methyl-D-aspartate (NMDA) receptor-mediated currents. Control slices (•) from day 11 (*A*) and day 15 (*B*) consistently showed LTP after tetanus, whereas slices bathed in APV (+) consistently failed to do so. The magnitude and time course of LTP over 30 min were not significantly different between the 2 ages.

Slices from five additional animals were tetanized in the absence or the presence of 25–100 μM D,L-2-amino-5-phosphonovaleric acid (APV), an antagonist at the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptor that prevents the induction of LTP in adult hippocampus. Representative records are shown for two slices each from a postnatal day 11 (Fig. 1*A*) and a postnatal day 15 (Fig. 1*B*) animal. In the presence of APV no potentiation

occurred, suggesting that NMDA receptor blockade prevents induction of LTP at these ages, as it does in adults.

Duration of LTP at days 11 and 15

At day 11 the posttetanus response was monitored for 60–400 min in the 11 slices that showed potentiation. Nine of the slices declined to the pretetanus baseline by 80–160 min posttetanus; the other two nearly reached baseline but were monitored for too short a time to determine when baseline was reached. At day 15 the posttetanus response was monitored for 30–500 min in the 11 slices that showed potentiation. Four of these slices declined to baseline by 130–240 min posttetanus. Four of them did not decline to baseline during the 320- to 500-min posttetanus recording period. In three day 15 slices stable posttetanus recordings were not obtained for sufficient time to evaluate whether they declined to baseline.

Sample response patterns at day 11 and day 15 are illustrated in Figs. 2, *A* and *B*, respectively. In Fig. 2*C*, average responses are plotted from day 11 and day 15 for which the posttetanus monitor was complete over the first 2.5 h. At each of the seven time points the mean of five consecutive measurements from each slice was extracted and averaged across animals. Over the first 60 min posttetanus, there were no significant differences in the magnitude of LTP. At all time points beyond 60 min posttetanus, the magnitude of LTP at day 11 was found to be significantly less than at day 15 ($P < 0.05$).

At day 15, the potentiated response generally persisted for longer than at day 11 and there was considerably greater variability in the pattern of endurance. The three examples illustrated in Fig. 3 show the range in response patterns. Over 6 h, the responses could be seen to decline to baseline (Fig. 3*A*), decline to a potentiated plateau (Fig. 3*B*), or remain elevated at a constant level (Fig. 3*C*). It is noteworthy that the two slices from Fig. 3, *A* and *C*, are from the same animal, and that the one shown in Fig. 3*A* was done first. The other two slices that did not decline to baseline by 6 h had intermediate response patterns similar to that in Fig. 3*B*.

Reinduction of LTP at day 11

At day 11, eight of the slices were retetanized after the potentiated response returned to baseline to assess whether the decline is associated with a return in the capacity for potentiation. The retetanization succeeded in producing a second potentiation in four of these slices (Fig. 4). In the other four slices, the response remained stable, but showed no repotentiation. The second potentiation was of a similar magnitude to the first; however, the time course was variable. In two of these slices the repotentiation declined to baseline over the subsequent 2 h (Fig. 4*A, part 2*), although a third tetanus delivered in one case, resulted in a more enduring potentiation (Fig. 4*A, part 3*). In the two other slices the second potentiation was more enduring (though apparently more variable) than the first, and did not return to baseline during the course of the experiment (Fig. 4*B, part 2*). These experiments also served as a control, suggesting that the decline is not the result of slice deterioration over longer recording periods.

DISCUSSION

The differences between postnatal days 11 and 15 in both the pattern and duration of potentiation demonstrate the rapid pace with which LTP changes during development. At day 11, potentiation can be induced but the response always returns to baseline by 2.5 h posttetanus. Just 4 days later at day 15 a potentiated response can endure for ≥9 h. Thus the capacity for induction of a *nonpersistent* LTP is present developmentally before the capacity for *persistent* LTP. Importantly, the pattern of LTP observed at day 11 is distinct from STP, which lasts for ≤30 min, and it is not the same as mature LTP, which lasts well beyond 2.5 h (Madison et al. 1991; Malenka 1991). These findings suggest that distinct temporal phases of LTP may appear stepwise during development and that in the developing animal these different phases can be observed without the pharmacological manipulations presently required to observe temporal phases in the mature hippocampus (Bliss and Collingridge 1993; Colley et al. 1990; Davies et al. 1989; Frey et al. 1988; Matthies 1991; Reymann et al. 1988).

Four processes that might have been responsible for these developmental differences in LTP are unlikely to be the causes, for the reasons discussed here. First, the decline in potentiation observed by 2.5 h posttetanus at day 11 and by 4 hours posttetanus at day 15 is unlikely to be due to deterioration of the slices because good physiological responses continued to be obtained for >6 hours posttetanus, because the duration of potentiation was not related to the total time spent in vitro (range: 4–23 h), and because LTP could be reinduced after the decline in potentiation. Second, it is unlikely that the decline in potentiation was caused by an underlying long-term depression induced by the slow, repetitive test stimulation (Stanton and Sejnowski 1989), because changing the pattern of test stimulation did not alter the potentiation. Third, it is unlikely that developmental differences in inhibition account for the shorter maintenance of LTP at day 11 because at day 15, when LTP is more persistent, there is also stronger synaptic inhibition (Bekenstein and Lothman 1991a; Harris and Teyler 1983; Muller et al. 1989; Swann et al. 1989). Fourth, it is unlikely that the ontogeny of the NMDA receptor is responsible for the changes in LTP observed between day 11 and day 15. Even though the density and properties of the NMDA receptors suggest that LTP should be more readily induced at day 15 than at day 11 (Insel et al. 1990; Kleckner and Dingledine 1991; McDonald et al. 1990), our findings show that LTP can be readily induced at day 11, that it is probably APV sensitive, and that it lasts for ≥1 h. In the mature hippocampus, insufficient activation of the NMDA receptor results in a potentiation that lasts only 10–30 min posttetanus (Malenka 1991). Therefore it is reasonable to conclude that the persistence of LTP, not its induction, is the primary difference between these ages.

Does the change in persistence involve a simple increase in duration of LTP with age, or is there a switch from an immature nonpersistent pattern to a persistent pattern of LTP? There does appear to be an increase in the duration of the immature, nonpersistent pattern of LTP between these ages from ~2 to 4 h. However, because all of the instances of nonpersistent LTP occurring at either day 11 or day 15

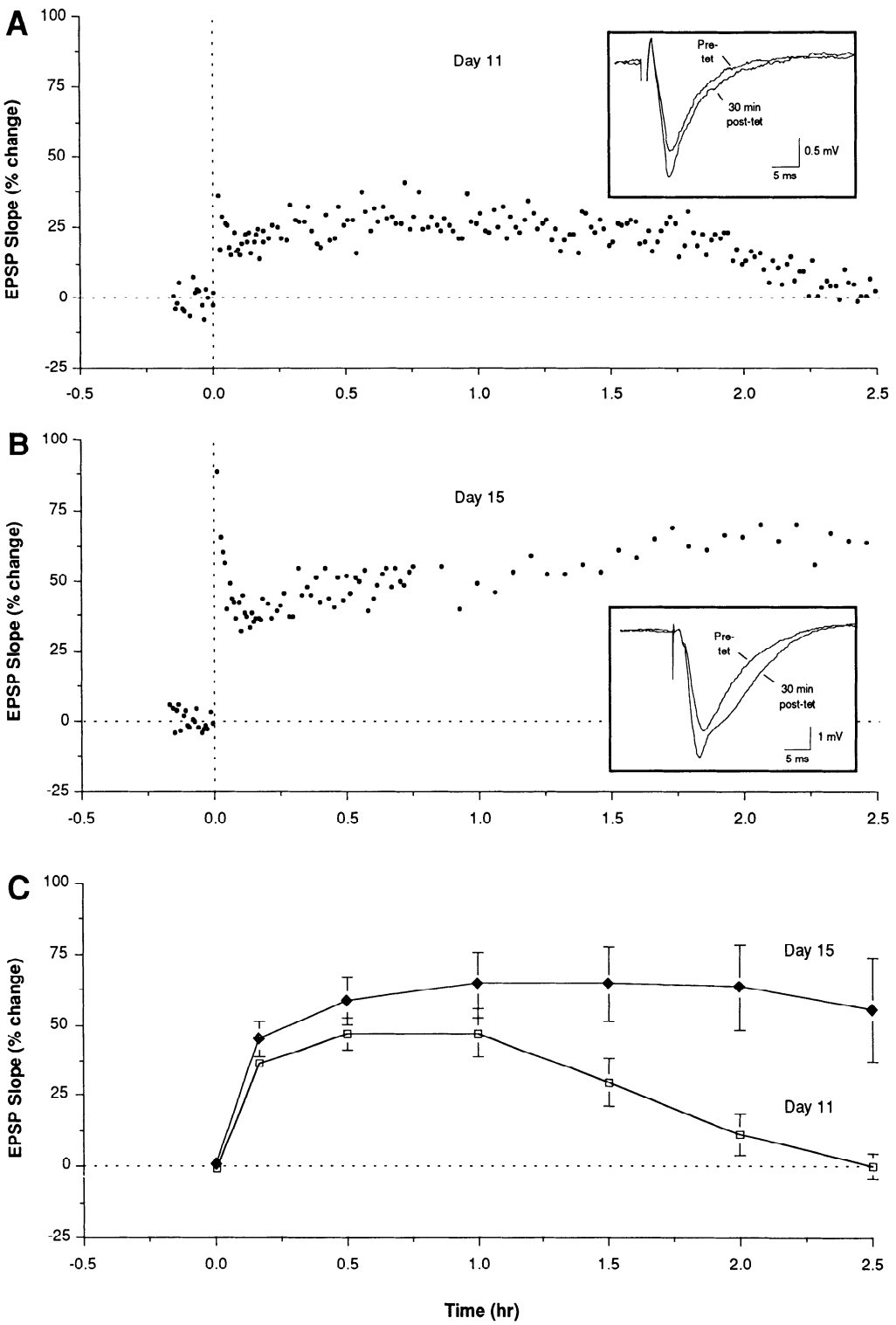

FIG. 2. Differences in the time course of LTP at days 11 and 15. In these experiments, responses were monitored for 2.5 h posttetanus. *A*: response from this day 11 slice remained potentiated for 1.5 h posttetanus, then declined over the next hour to baseline. *B*: response from this day 15 slice remained potentiated for >2.5 h. *C*: average (mean ± SE) responses from day 11 (□, $n = 9$) and day 15 (♦, $n = 8$) slices at pretetanus and 6 time points posttetanus. Data at time 0 are the pretetanus mean.

declined to baseline by 4 h, and all of the instances of persistent LTP at day 15 remained potentiated even at 5–8 h posttetanus, there appears to be a rapid switch between the nonpersistent and persistent forms of LTP. These observations suggest that there is a developmental threshold that must be reached before the onset of persistent LTP, and that this threshold may be reached at different postnatal days by different animals. The differences between animals may depend on previous experience or other factors. Furthermore, because reinduction of LTP at day 11 can lead to a more persistent potentiation than was induced by the first tetanus, it may be possible that induction of LTP itself

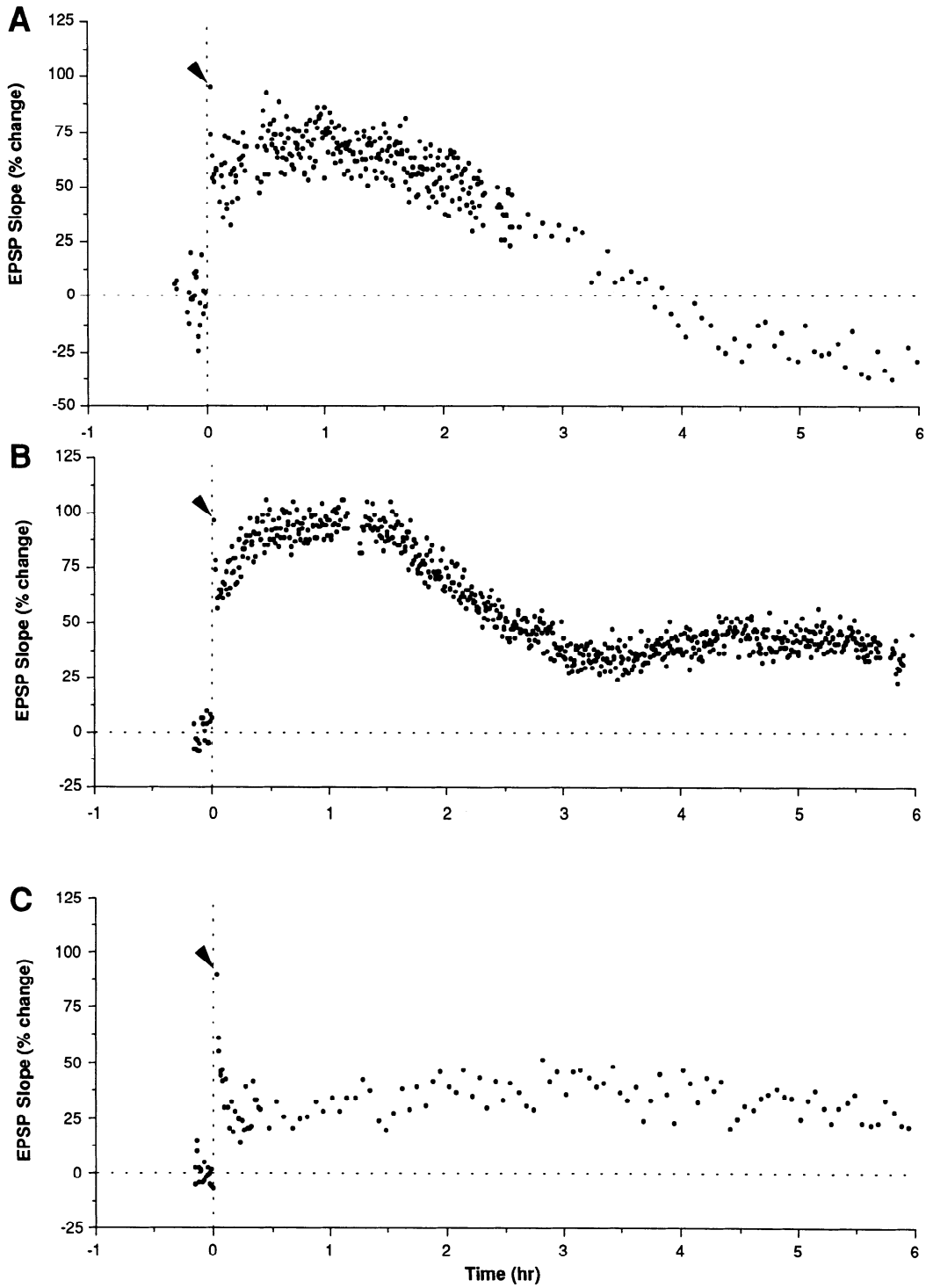

FIG. 3. LTP at day 15 monitored for 6 h posttetanus. *A*: in this slice the response remained consistently potentiated for 1.5 h then began a gradual decline to reach a new baseline slightly below the pretetanus baseline by 4 h where it remained for the duration of the experiment. This response pattern resembles that seen in day 11 slices over a time scale approximately twice as long. *B*: in this slice the response began to decline 2 h posttetanus, but then stabilized by 3 h at a level significantly potentiated compared with the pretetanus control. The response remained at this level for the duration of the experiment (>8 h posttetanus). *C*: this record shows a response that remained potentiated at a constant level for the duration of the experiment. In each of the records, a brief posttetanic potentiation occurred (▶).

could have a "priming" effect on the neurons, thereby evoking cellular processes that are necessary for the switch from nonpersistent to persistent LTP.

Several cellular processes could account for the developmental switch in the duration of LTP. Of particular interest is the observation that LTP measured in adults has three distinct temporal phases with different sensitivities to inhibition of protein kinase C or protein synthesis (Colley et al. 1990; Davies et al. 1989; Frey et al. 1988; Matthies 1991; Reymann et al. 1988). The first phase lasts ~1.5 h, and is

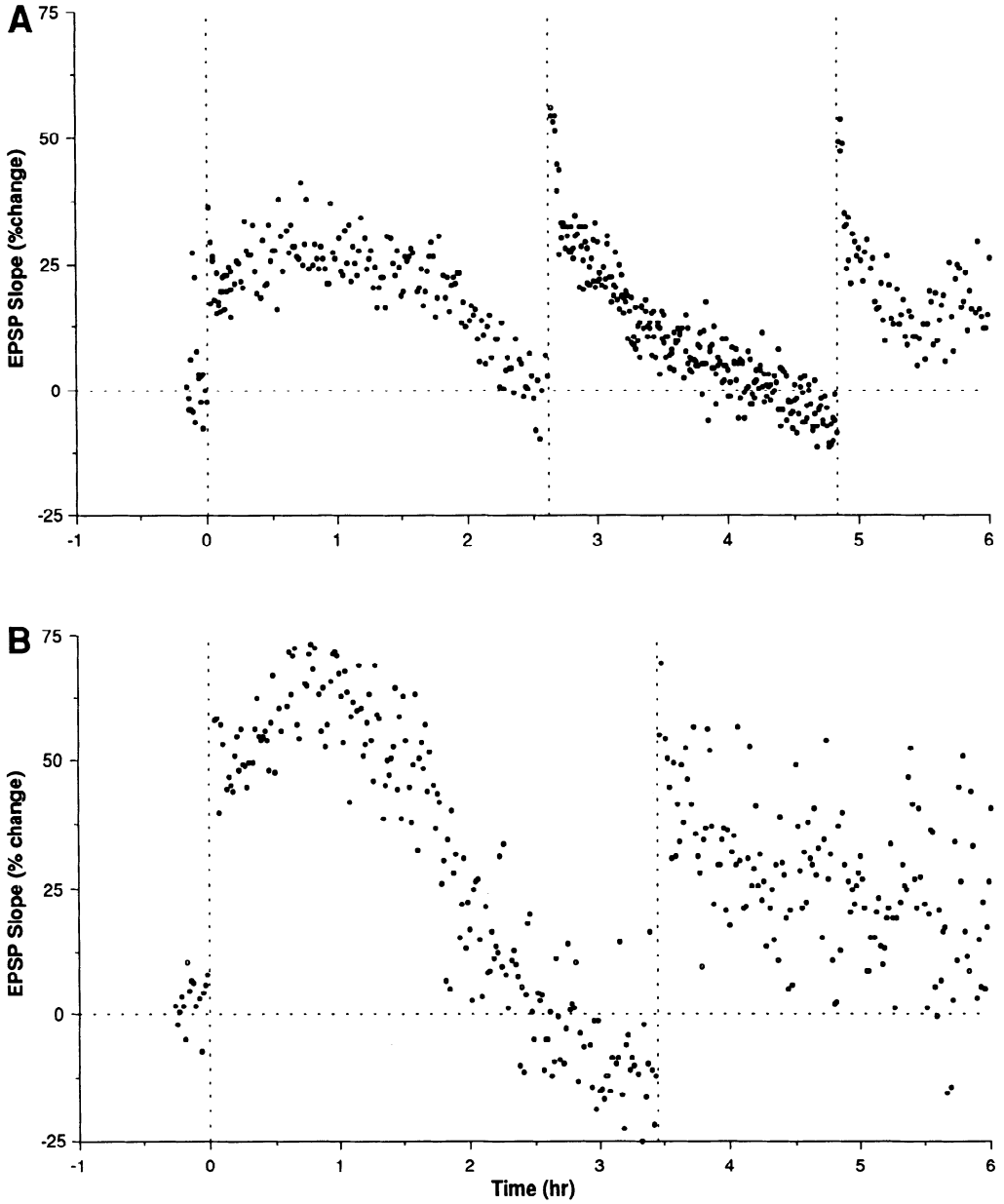

FIG. 4. LTP at day 11 can be reinduced. Slices from day 11 animals were monitored for ≥6 h posttetanus. Tetanic stimulation was delivered at time 0. Posttetanic responses were monitored until the response returned to the pretetanus baseline, at which time the slices were retetanized. All tetani are indicated by vertical dotted lines. All responses are normalized with respect to the 1st pretetanus baseline. *A*: in this slice, the initial potentiation declined to baseline by 2.5 h at which time the slice was retetanized. The 2nd potentiation remained above baseline for ~1 h. After decline of the 2nd potentiation, the slice was tetanized for a 3rd time at 4.75 h (2.25 h after the 2nd tetanus). The 3rd potentiation lasted for the duration of the experiment (1.25 h). *B*: in another experiment, the response returned to baseline after 2.5 h and stabilized slightly below baseline at 3 h. A 2nd tetanus was delivered at 3.5 h, which produced a potentiation that lasted for the duration of the experiment (2.5 h).

not sensitive to inhibition of protein kinase C. The second phase lasts ~5 h, and is sensitive to inhibition of protein kinase C. The final phase lasts indefinitely, and is sensitive to inhibition of protein synthesis. The time courses of these phases are strikingly similar to those of nonpersistent LTP in day 11 rats, of nonpersistent LTP in day 15 rats, and of persistent LTP in day 15 and adult rats, respectively. Thus the increase in duration of the nonpersistent LTP between day 11 and day 15 could involve alterations in protein kinase C. Indeed, protein kinase C in general shows the largest increase in its expression between day 7 and day 15, and whole brain preparations show a particularly dramatic increase in the neural specific, gamma subspecies over this time period (Hashimoto et al. 1988; Yoshida et al. 1988). Correspondingly, the switch from nonpersistent to persistent LTP that seems to occur near day 15 could involve the development of the capacity for appropriate protein synthesis during LTP (i.e., see Jensen et al. 1993).

LTP may be further influenced by the rapid pace of synaptogenesis and the formation of dendritic spines occurring during development. The density of dendritic spines on CA1 pyramidal cells increases 2.5-fold between days 10 and

20 (Zimmer 1978). A shift occurs from predominantly shaft synapses at day 7 to spine synapses, some of which have constricted necks, at day 15 (Harris et al. 1989, 1992). There is a further twofold increase in spine synapses between day 15 and adults, and nearly all of the adult spines have constricted necks. The presence of constricted necks might serve to reduce the diffusion of LTP-specific molecules away from the potentiated synapses (Gamble and Koch 1987; Koch et al. 1992; Zador et al. 1990) such that sufficient levels can be maintained to achieve persistent LTP (Harris and Kater 1993).

The beginning of the third postnatal week is an active time in the development of the rat hippocampus. Regarding LTP, the results presented here suggest that the immature animals are neither a homogenous group nor equivalent to adult animals in terms of the time course and the cellular mechanisms of potentiation induced by tetanus. It is clear that LTP must be monitored for > 1 h posttetanus to establish whether it is persistent, and possibly to distinguish the different pre- and postsynaptic mechanisms that could predominate during the different temporal phases. In addition, it is important to consider that grouping animals into age ranges could obscure rapid developmental shifts in the expression of LTP. Further physiological, biochemical, and morphological characterizations of LTP during ontogeny will be required to elucidate which cellular mechanisms are responsible for the shifts in expression and persistence of LTP that occur during development.

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