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THE DEVELOPMENT OF LONG-TERM POTENTIATION IN HIPPOCAMPUS AND NEOCORTEX

T. J. TEYLER, A. T. PERKINS, IV* and KRISTEN M. HARRIS†

*Neurobiology Department, Northeastern Ohio Universities, College of Medicine, Rootstown, OH 44272, U.S.A.; and †Neuroscience Department, Children's Hospital, Boston, MA 02115, U.S.A.

Abstract—The development of long-term potentiation (LTP), an enduring alteration in synaptic efficacy following afferent activation, was examined in CA1 hippocampus and primary visual cortex of rat. Both regions show little LTP prior to postnatal day 5, demonstrate a maximal potentiated response around postnatal day 15, and a subsequent decline to adult levels. These results are discussed with respect to the underlying mechanism of action and behavioral significance of these critical-period phenomena.

INTRODUCTION

THE MECHANISM(S) by which the mammalian central nervous system registers and stores learned information is currently the subject of considerable attention. Long-term potentiation (LTP) is a long-lasting enhancement of the response of hippocampal and other mammalian neurons that is widely studied as a useful mnemonic mechanism because its induction, expression, and duration mimic many properties associated with learning and memory [5, 32, 42, 43, 44]. Although the hippocampus has been the favored neural structure for studies of LTP since its discovery in the early 1970's, other mammalian CNS structures, including neocortex, show similar synaptic plasticity [44, 47].

An important question to be considered when examining different synaptic regions of the mammalian CNS is whether or not these similar expressions of synaptic modification reflect the same underlying cellular mechanisms. Whereas it is entirely possible that nature would conserve neuronal mechanisms to be employed in plastic modifications of synapses, there is little hard evidence to support such a contention. Thus, it is equally possible that different forms of plasticity may be represented not only across species, but also in different brain regions of a single species.

The present article will examine the phenomenology of LTP in terms of its developmental characteristics in two tissues of the rodent brain—the hippocampus and neocortex. While sufficient information has not yet been accumulated to permit a mechanistic analysis of the similarities of LTP at synapses in these two regions, it is possible to compare the characteristics and dynamics of LTP across development. Such a comparison is useful not only in terms of eventually determining if the underlying mechanism of LTP is common to all plastic synapses, but also in terms of understanding the respective roles of hippocampus and neocortex in memory functions.

This study was motivated by our earlier observations that hippocampal area CA1 showed a much greater magnitude of potentiation early in development than in adults. This peak in LTP magnitude occurred at postnatal day 15 (P15), a time when the eyes first open and animals are actively exploring their environments. Our goal was to determine whether the

visual cortex might exhibit a similar course of LTP development, particularly since this is a time of maximal sensitivity for visual plasticity [11, 38].

Long-term potentiation

LTP is an increase in synaptic efficacy brought about by a brief afferent tetanus or by behavioral learning [44]. In area CA1, LTP induction requires the precise pairing of presynaptic release of neurotransmitter (glutamate or aspartate) with sufficient depolarization of the postsynaptic cell. The neurotransmitter activates specific glutaminergic receptors, referred to by their selective agonist *N*-methyl-D-aspartate (NMDA), when sufficient postsynaptic depolarization releases the magnesium block of NMDA-associated calcium channels [10, 18, 34, 41]. Calcium entry to the post- and/or presynaptic sites initiates other processes, not yet fully understood, that lead to the expression of LTP [14]. LTP is expressed as an increase in the response of the postsynaptic cell to a constant afferent stimulus [3, 39, 44]. This enhanced response can endure for hours, days, weeks and longer, depending on the exact stimulus parameters employed, how often LTP is induced at the same synapses, and the age, health, and behavioral experience of the animal at the time LTP is tested [1, 20, 27, 33].

Presynaptically, there is evidence for an enhanced release of neurotransmitter at hippocampal synapses [5, 40]. Postsynaptically, an enhanced synaptic conductance occurs, which could be mediated by several cellular mechanisms [3, 18]. The number or binding activity of glutaminergic receptors that primarily open Na^+ or K^+ channels (kainate or quisqualate selective) [19] might increase to provide enhanced conductance [24]. An increase in the length of the postsynaptic density [12, 37] could reflect an increase in the availability or expression of some or all of the 20–30 proteins found there [22, 23, 31] and thought to be involved in LTP [13]. Shortening and widening of long and thin spine necks would provide a simple geometrical mechanism for the enhanced synaptic conductance occurring with LTP [15, 16]. Other studies suggest a decrease in the variability of spine shape, which has been interpreted to be a rounding of the spine head following LTP, though it is unclear how this would affect synaptic transmission [9, 28, 46].

Comparatively little is known about the parameters, mechanisms or distribution of neocortical LTP. LEE [28] has shown that brief tetanic stimulation (400 Hz, 0.5 sec) of afferents located in the white matter of visual cortical slices from adult rats results in 15–20% potentiation of the evoked response. In a parametric investigation of LTP induction in supragranular layers of developing rat visual cortex, BERRY *et al.* [4] report that low intensity, low frequency stimulation yields greater postsynaptic response potentiation than does high intensity, high frequency stimulation—which often results in response depression. In visual cortical slices obtained from kittens between the ages of 2 weeks and 6 weeks, KOMATSU *et al.* [25] demonstrated substantial LTP (200–500%) following stimulation of 2 Hz for 1 hr. Here, the higher magnitude LTP occurs via polysynaptic activation of supragranular layers of cortex and the lower magnitude LTP occurs in the monosynaptic response recorded in the infragranular layers. It appears that LTP phenomena in neocortex display complexities not present in simpler tissue like hippocampus. Such complexity may be the result of heterogeneous cell populations and/or afferents selectively activated, or may represent the complex integrative properties of the tissue.

Studying LTP ontogeny is hampered by uncertainties regarding the parametric requirements of LTP at different ages. While it would be possible to examine exhaustively a wide spectrum of tetanic stimulation parameters for each age, the solution adopted here was

to utilize those parameters proven to be optimal for adult potentiation, and to apply those parameters throughout development. Such a procedure offers the advantage of utilizing a standard pattern of afferent activation of all synapses under study. Comparing the sequence of LTP ontogeny in these two brain regions provides a good opportunity to begin assessing how this important physiological plasticity might serve to influence or be influenced by synaptogenesis and the onset of behavioral function.

METHOD

Detailed methods for studying the ontogeny of hippocampal LTP have been reported [20]. Briefly, hippocampal slices were obtained from rat pups at days P1–8, 10, 15 and 60–64 and maintained at the interface of medium (Earles balanced salt media with glucose) and a warm (30–34°C) humid atmosphere (95% O_2/5% CO_2). A concentric bipolar stimulating electrode was placed in the Schaffer collaterals of stratum radiatum and a recording electrode placed in the stratum pyramidale. Stimulation intensity was adjusted to give a 1 mV population spike. Following determination of a stable baseline, tetanus was delivered at 100 Hz for 1 sec. Changes in synaptic efficacy were monitored for 20 to 100 min post-tetanus. Control experiments consisted of the presentation of the same stimuli, but at a frequency of 1/15 sec.

Neocortical area 17 (visual cortex)

Neocortical slices from area 17 (visual cortex) were obtained from female Long Evans rat pups at days P1–5, 6–10, 11–15, 16–20, 21–25, 26–30 and 60–90. Stimulation was delivered by a concentric microbipolar electrode to the subjacent white matter, activating afferents coursing into the cortical gray matter. Field potential recordings were made 300–500 μm medial to the site of stimulation from the pial surface to the white matter. Tetanic stimulation was delivered to the white matter at a frequency of 2 Hz for 10 min. The post-tetanic response was monitored at a single recording site for 2–3 hr and a complete transcortical recording profile was obtained at the end of the experiment. More details are provided in PERKINS and TEYLER [36].

RESULTS

Ontogeny of LTP in hippocampal area CA1

LTP, measured as an enhanced population spike response at 20 min post-tetanus, first occurred at P5 and was seen consistently by P7–8 in hippocampal area CA1. The magnitude of LTP at P15 was considerably greater than that observed earlier or at adult ages (Fig. 1). We considered whether this peak in LTP magnitude could be explained by greater excitability of CA1 pyramidal cells at P15 than in the adult. Several measures of pretetanus pyramidal cell excitability were tested. The voltage required to elicit a threshold field EPSP was greater in young animals than in adults. The maximal population spike amplitude increased with age. The population spike latency decreased with age. The field EPSP slope at population spike threshold was greater at P15 than in adults. Together these findings suggest that pretetanus excitability is greater in the adults than at P15.

Ontogeny of LTP in neocortex

LTP in infragranular layers of cortex (IV–VI), measured here as an enhanced polysynaptic evoked response, first occurred an P6 and was seen consistently by P11–20 (Fig. 2). The magnitude of LTP of the infragranular response was much greater at P16–20 (215% of baseline) than at older ages (130% at P60–90). The short latency, presumably monosynaptic evoked responses, showed little change following tetanic stimulation.

LTP of the field potential in the supragranular layer (layers I–III) also first occurred at P6 and was seen consistently by P11–15. In this layer, the magnitude of LTP was greatest between P16–20 (180%), with a subsequent decline in adults (120%).

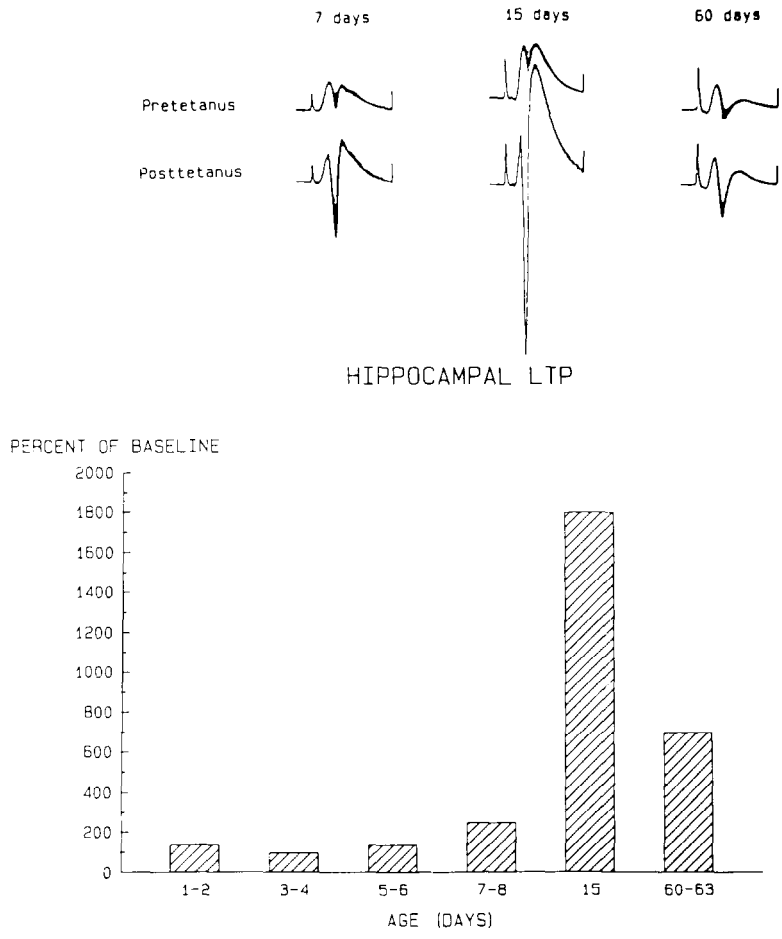

FIG. 1. The post-natal development of long-term potentiation in hippocampal area CA1. LTP, measured as an enhanced population spike response expressed as a percent of pretetanus baseline (100%), first appears at postnatal day 5 and peaks at day 15; adapted from [20] (calibration, 1 mV).

DISCUSSION

These studies show that both hippocampal area CA1, and infragranular and supragranular layers of the visual cortex have developmental periods of peak sensitivity to tetanic stimulation. Both regions show little LTP prior to P5, a peak magnitude around P15, and a subsequent decline to adult levels.

The absolute magnitude of LTP is difficult to compare between these two brain regions because of differences in their cellular architecture that can cause differences in the magnitude of the extracellular evoked response recorded. The highly ordered termination of afferents onto hippocampal dendrites leads to large and clearly defined current source/sink relationships and associated field potentials. In contrast, the more heterogeneous and complex distribution of afferent input to cortical cells results in less well defined source/sink relationships, and smaller field potentials. The packing density of hippocampal pyramidal cells is much higher than that of cortical cells, which further facilitates recording of more

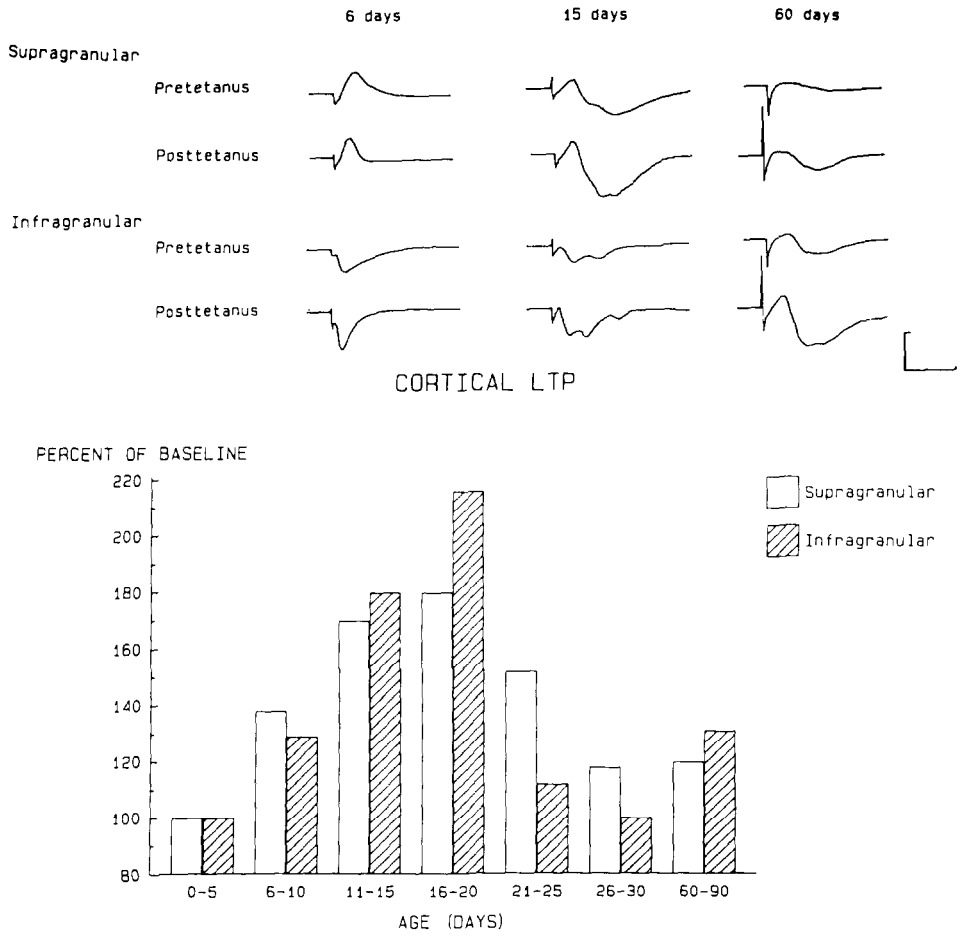

FIG. 2. The postnatal development of long-term potentiation in cortical area 17. Recordings were made at supragranular and infragranular areas before and after tetanic stimulation of the subjacent white matter. LTP, measured as an enhanced field potential expressed as a percent of pretetanus baseline (100%), first appears at post-natal day 6 and peaks at days 16–20 in both areas; adapted from [36] (calibration, 0.5 mV, 10 msec).

robust field potentials in the hippocampus than in the cortex. Therefore, the differences in absolute magnitude of LTP measured in these two regions at varying developmental stages might simply reflect differences in the difficulty of obtaining well-synchronized responses of the cells.

With these reservations in mind, it is instructive to note that the magnitude of the post-synaptic change seen in neocortical LTP is approx. 250% (baseline equals 100%). The magnitude of hippocampal LTP is approximately five times greater during the same period (~ 15 days). Adult levels of hippocampal vs neocortical LTP also show differences favoring the larger magnitude hippocampal response (post-tetanus increase by a factor of 6) as compared to the neocortical change (post-tetanus increase by <2). While these data would appear to suggest that the magnitude of LTP is considerably greater in the hippocampus than neocortical tissues, such a conclusion may be unwarranted for the reasons mentioned

above. Additionally, it is quite conceivable that the stimulation of white matter afferents in the neocortical slice also activates plastic as well as non-plastic synapses, thus considerably reducing the signal-to-noise ratio (although such a contention can be raised for hippocampus as well). Thus, it is difficult to compare directly hippocampal and neocortical post-synaptic responses. Nevertheless, the parallel in the ages of LTP onset and peak between these two regions suggests a strong relationship of LTP in both regions to the onset of active exploration of the environment.

There are several possible mechanisms for shifts in LTP magnitude that occur with maturation. Anatomical studies show that laminar differentiation of cortical layers V and VI does not occur until day 6 in the rat visual cortex [35]. This coincides with the first age that a tetanus elicited LTP in this study. The spine density of layer IV pyramidal cells increases drastically between days 8–16, reaching adult levels by the fourth postnatal week. This increase in pyramidal cell spine density coincides with our largest LTP magnitude (11–20 days). Immediately after the surge in pyramidal cell spine density, non-pyramidal cell spine density reaches a maximum (by the third week), declining to adult levels by the fourth postnatal week. During the third week supernumerary spines are present on non-pyramidal cells; these spines are subsequently resorbed during the fourth week, resulting in a loss or possible redistribution of synaptic contacts.

In kitten neocortex, NMDA receptors are more sensitive to blockage than in adult cats, suggesting that the NMDA receptors might be more effective during development than in the adult, and might mediate an enhanced developmental LTP [45]. A similar enhanced response of NMDA receptors occurs during hippocampal development (Hamon and Heinemann, personal communication). Preliminary results suggest that at P15, more dendritic spines are short and stubby than in adults—whose spines are longer and thinner [21]. Between P15 and adulthood, the synaptic surface of stubby spines increases in area (stratum radiatum of CA1) [21].

Together, these findings suggest that the enhanced responsivity of the NMDA receptors could occur on developing stubby dendritic spines that are less likely to attenuate current generated at quisqualate or kainate receptors at P15. Perhaps LTP expression and duration are also associated with synaptic growth, and the stubby spines with perforated synapses represent the growing synapses and spines, many of which have reached a maximum size in adults, so that fewer are available for LTP induction. Thus, LTP might be related to some aspect of synaptogenesis, such that newly formed synapses are "plastic" and capable of developing LTP. Potentiated synapses, however, are removed from the available pool of plastic synapses as the animal matures [20].

Significance of critical periods of LTP

Both hippocampal and neocortical synapses appear to demonstrate a critical period for optimal induction of LTP under the parameters used in these experiments. The period when maximal hippocampal and visual cortical LTP can be elicited corresponds to a time when many behaviors are first experienced by developing pups. Young rats are first experiencing patterned visual stimuli during this time, which coincides with the maximal period of visual plasticity during development [11, 38]. With respect to the behavioral significance of a critical period for LTP in developing hippocampus, it should be noted that the behavioral repertoire of the rodent is rapidly expanding at this time. The central nervous system is being exposed for the first time to patterned visual and auditory stimulation [2], voluntary movements and exploratory behavior are predominant [26], and retention of some forms of

learned behavior has reached adult values by postnatal day 15 [7]. To the extent that the hippocampus is involved in coding these environmental influences, the pattern of the hippocampal LTP thus mirrors these important developmental behavioral milestones. Thus, these data support the hypothesis that CA1 LTP develops in parallel with the onset of exploratory behaviors in the rat—a time when the animal is learning much about its environment. Future experiments could test this hypothesis by manipulating the environment such that the critical period of visual plasticity is altered, thus predicting an alteration in the critical period for LTP.

In the infragranular layers of the neocortex, the re-emergence of LTP in the adult animal, following levels of near baseline potentiation between 21 and 30 days of age, may reflect the activation of different populations of afferents or targets at these two times. Alternatively, the plastic properties of the synapses may undergo modulation by unknown factors during this period. The identity of the cortical synapses undergoing plastic modification cannot be addressed with the present data. Whereas it is probable that many infragranular afferents arise from thalamocortical systems terminating in layers III and IV [30] and that supragranular afferents are composed of both callosal fibers [8] and ipsilateral associational fibers [17], it is unknown to what degree these dominant inputs are responsible for the plastic changes observed. Further studies will be required to identify better the synapses responsible for the observed modifications.

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