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Developmental Brain Research 148 (2004) 11–18
DEVELOPMENTAL BRAIN RESEARCH
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Research report

Alterations in synaptic transmission and plasticity in area CA1 of adult hippocampus following developmental hypothyroidism☆

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Accepted 29 September 2003

Abstract

Transient reductions in thyroid hormone during critical periods of brain development can have devastating and irreversible effects on neurological function. The hippocampus is a brain region sensitive to thyroid hormones and is a necessary substrate for some forms of learning and memory. Subregions within the hippocampus display distinct ontogenetic profiles and have shown differential vulnerability to some indices of thyrotoxic insult. Synaptic function can be readily assessed in the hippocampus, yet little information exists on the consequences of early thyroid hormone insufficiency on the neurophysiological integrity of this structure. Previous work has examined the long-term consequences of perinatal hypothyroidism on neurophysiology of the dentate gyrus of the hippocampal formation. The current study reveals that alterations in synaptic function also exist in area CA1, and some differences in the pattern of effects are evident between the two hippocampal subfields. Developing rats were transiently exposed to the thyrotoxicant, propylthiouracil (PTU; 0 or 15 ppm), through the drinking water of pregnant dams beginning on gestational day 18. This regimen markedly reduced circulating levels of thyroid hormones and stunted pup growth. PTU exposure was terminated on postnatal day (PN) 21 and electrophysiological assessments were conducted by recording field potentials in area CA1 of hippocampal slices derived from adult male offspring. Synaptic transmission, short-term, and long-term synaptic plasticity were assessed. Consistent with observations in the dentate gyrus, somatic population spike amplitudes were reduced in assessments of baseline synaptic transmission of slices from PTU-exposed animals. No differences were identified in excitatory postsynaptic potentials (EPSP). Short-term plasticity of the EPSP as indexed by paired pulse facilitation was markedly impaired by PTU exposure. Long-term potentiation (LTP) of the population spike was enhanced, consistent with findings in dentate gyrus, but no change in EPSP LTP was detected. Perturbations in synaptic function in the hippocampus of adult rats transiently exposed to a period of hormone insufficiency during the perinatal period are likely to contribute to cognitive deficits associated with developmental hypothyroidism.

Theme: Development and regeneration
Topic: Hormones and development

Keywords: Propylthiouracil; Hippocampus; Long-term potentiation; CA1; Synaptic transmission; Paired pulse facilitation; Neuroplasticity; Ex vivo; Developmental

1. Introduction

Thyroid hormones are essential for maturation and function of the mammalian central nervous system (CNS). Deficiencies in thyroid hormone during brain development produce reductions in myelination, impairments in proliferation and migration of cells, hyperplasia of the arborization of dendrites and axons, and retardation of synapse formation [5]. Perinatal reduction in circulating levels of thyroid hormones leads to growth retardation, neurological deficits, and impaired performance on a variety of behavioral learn-

☆ The information in this document has been funded in part by the US Environmental Protection Agency. It has been subjected to review by the National Health and Environmental Effects Research Laboratory and approved for publication. Approval does not signify that the contents reflect the views of the Agency, nor does it mention of trade names or commercial products constitute endorsement or recommendation for use.

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doi:10.1016/j.devbrainres.2003.09.018

ing tasks [1,13,41]. Thyroid hormones exert tissue- and cell-type specific effects such that the "critical window" for thyroid hormone deprivation on brain development cannot be readily defined as it is dependent upon the ontogeny of the particular neural substrate under study. Neither is the influence of thyroid hormones on developmental processes uniform across all brain regions with the same maturational status or at different times during development [47]. As a result, the phenotype of neurological impairment is a product of the duration, the timing, and the severity of interruption of specific thyroid-hormone-dependent processes in particular brain regions [47].

The hippocampus is a brain region-dependent upon thyroid hormone for maturation and function in developing and adult organisms [18,21,26–28]. It comprises three specific subfields, each with distinct ontogenetic profiles. In the rodent, neurogenesis is primarily a prenatal event for the principal cells of area CA1 and CA3, whereas dentate gyrus granule cell birth peaks during the second postnatal week [4]. Although dendritic arborization, synapse formation, and synaptic refinement continue postnatally in the pyramidal cell subfields of area CA1 and CA3, these processes begin in the prenatal period and precede by several weeks similar events in the dentate gyrus [4]. In addition to distinct ontogenetic profiles, subregions within the hippocampus exhibit differential vulnerabilities to some indices of thyrotoxic insult [22,24]. Impairments in synaptic transmission and plasticity in the dentate gyrus of adult animals experiencing a brief period of neonatal hypothyroidism have recently been reported [19]. The purpose of the present study was to expand upon these observations and assess the long-term consequences of hormone insufficiency on synaptic function of the CA1 subfield of the hippocampal formation.

Previous work in area CA1 of hippocampal slices taken from hypothyroid animals early in development has revealed an enhancement of synaptic transmission, impairment in long-term synaptic plasticity [34,43] and reductions in short-term plasticity [43,46]. In these studies, the permanence of the effects was not established such that the functional impairments that derive from organizational/structural changes in brain ontogeny as a consequence of developmental insult cannot be readily dissociated from the acute pharmacological effects that 'absence of hormone' may have on physiological function. A recent report reveals irreversible deficits in the dentate gyrus following transient hormone insufficiency [19]. However, Vara et al. [46] reported that a single hormonal supplement is sufficient to reverse developmental impairments in synaptic function in area CA1. The present findings reveal a pattern of synaptic dysfunction in area CA1 which is permanent despite return of thyroid hormone to control levels at the time of assessment. Disruption of synaptic function and plasticity in two regions within this structure may collectively contribute to the cognitive deficits associated with developmental hypothyroidism [1,9,13,41].

2. Methods

2.1. Subjects

Pregnant Long–Evans rats were obtained from Charles River Laboratory (Raleigh, NC) on gestational day (GD) 14 and housed individually in standard plastic hanging cages with sterilized pine shavings as bedding in an AAALAC-approved animal facility. The colony room was maintained on a 12:12 light:dark schedule, and all animals were permitted free access to food (Purina rat chow) and tap water. The dams were administered 0 or 15 ppm propylthiourycil (Sigma) beginning on GD18 and continuing throughout lactation until postnatal day (PN) 21. All litters were culled to 10 pups on PN3, equal number of males and females where possible, and were weaned and housed 2/cage on PN30. Animals were weighed on PN7, PN14, PN21, PN30 and as adults. Males from each litter were used for in vivo electrophysiological assessments in the dentate gyrus prior to PN150 and results of these experiments are reported in Gilbert and Pazckowski [19]. A second group of male littermates was sacrificed for the present study between 7 and 11 months of age for electrophysiological assessments in area CA1 in vitro. Control and treated animals were assessed on alternate days such that the mean age at the time of testing was comparable between the groups. Data are comprised of animals from 9 control and 11 treated litters with 1–2 animals represented from each litter.

2.2. Thyroid hormone assay

Thyroid hormone levels were determined in blood sampled from animals at culling, at the termination of exposure (PN21) and at weaning (PN30). Trunk blood was collected following decapitation and serum was separated via centrifugation of clotted samples and stored at $-80\,^{\circ}C$ for later analyses by radioimmunoassay (Diagnostic Products, Los Angeles, CA). Serum concentrations of total T4 and total T3 were assayed as described by Sawin et al. [40]. All samples for total T4 and total T3 measurements were run in duplicate and the intra- and inter-assay variations were below 10%. Based on greater than 95% specific binding, the sensitivity of the radioimmunoassay for total T4 was 2.5 ng/ml. Results below this limit of quantification were recorded at 2.5 ng/ml for statistical purposes.

2.3. Slice preparation

Transverse hippocampal slices (400–450 μm) were prepared from adult male offspring according to standard procedures and were transferred to an interface recording chamber. During dissection and for the first 30 min of perfusion, slices were bathed in a high sucrose (50 mM) artificial cerebrospinal fluid (ACSF: 124 mM NaCl, 3 mM KCl, 2.0 mM $MgSO_4$, 2 mM $CaCl_2$, 1.25 mM NaH_2PO_4, 26

mM $NaHCO_3$, 10 mM glucose, pH 7.4) at 34 °C at a rate of 1.0 ml/min. Thereafter, the perfusion medium was switched to the standard ACSF and recording began 1–2 h later.

2.4. Electrophysiological recording

Biphasic squarewave pulses (Grass S-88) were delivered through a bipolar tungsten electrode placed in the stratum radiatum. In each slice, stimulation-evoked extracellular field potentials were recorded from the pyramidal cell layer and the stratum radiatum of CA1 through glass micropipettes (2–4 μm tip diameter) filled with ACSF. Responses were amplified, digitized (33 kHz sampling rate), averaged using LabWindows (National Instruments) and custom designed software, and stored on a PC for later analysis.

2.5. Waveform scoring

The dendritic responses recorded from the stratum radiatum provide an index of synaptic activity comprising the summed excitatory postsynaptic potentials (EPSP) [7]. The slope of the EPSP was calculated as the rate of amplitude change for the initial negative deflection at the dendritic site. EPSP peak was estimated by the voltage at the most negative point on the waveform and EPSP area measurements were derived from the area under the curve taken from the point of EPSP onset to the return to baseline (inset, Fig. 2A). Action potentials in pyramidal cell neurons are reflected in field potential recordings from the pyramidal cell layer as a large negative potential, the population spike [7]. Population spike amplitude was estimated at this site by the voltage difference between the most negative point of the spike and a line connecting the beginning of the spike and the next positive peak on the waveform (inset, Fig. 2B).

2.6. Data collection

Stability of baseline recordings was established by delivering single pulses (1/min, 0.1 ms pulse width at an intensity yielding half-maximal population spike amplitude for a given slice) for 15–30 min prior to collection of input/output (I/O) functions. Baseline synaptic transmission was assessed by averaging the response to 5 pulses delivered at a rate of 0.05 Hz at each of the 14 stimulus intensities ranging from 20 to 150 μA. Paired–pulse facilitation was examined at a range of interpulse intervals (IPIs; 20–1500 ms) and two stimulus intensities (half-maximal for elicitation of a population spike and maximal intensity of 150 μA). Paired-pulse data were expressed as a ratio of the second response amplitude relative to the first.

Following completion of paired pulse tests, LTP was evaluated by setting the stimulus intensity to that which produced 50% of maximal population spike amplitude. Twenty sweeps were collected at a rate of 1/min, the last 10 sweeps were averaged and comprised the pretrain baseline response to which all post-train values were compared. LTP was induced by delivering twenty-five 100-Hz train bursts (4 pulses/burst, 0.1 ms pulse width), at an interburst interval of 200 ms. Train intensities were those used for single pulse stimulation. Evoked potentials were sampled at 1-min intervals for the next 30 min to determine the

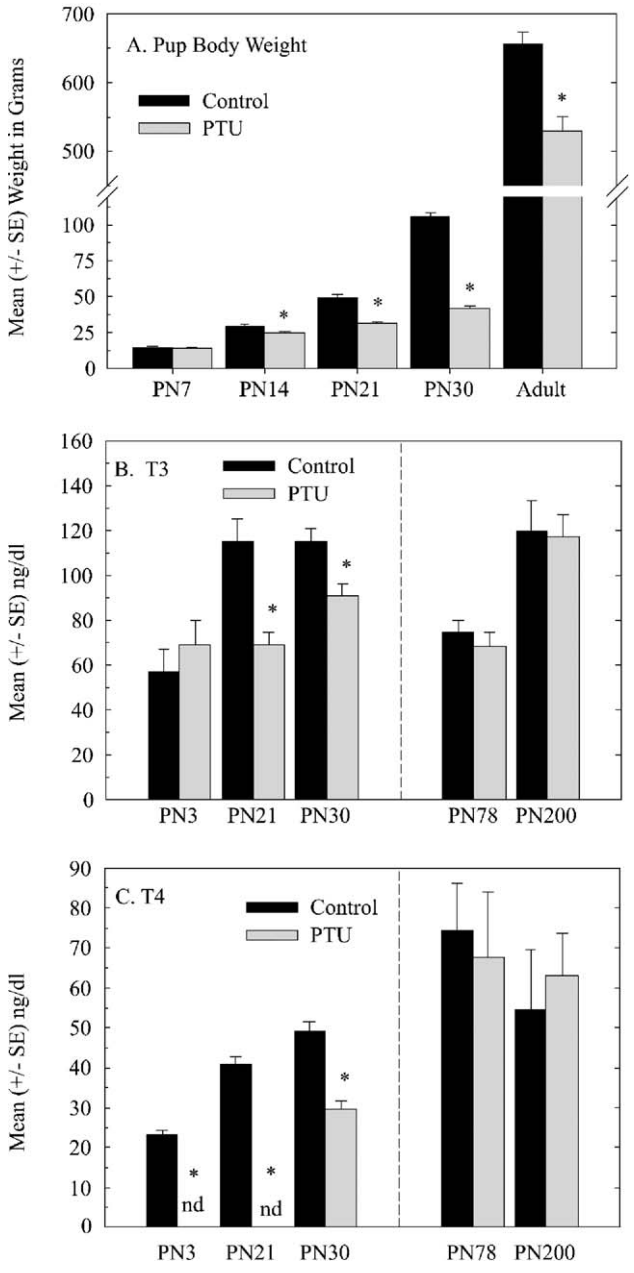

Fig. 1. Body weight and thyroid hormones are reduced by PTU exposure. (A) Mean weight (±S.E.M.) was reduced by postnatal day (PN) 14 in PTU-exposed animals and weight decrements persisted in adulthood. Mean (±S.E.M.) serum levels of thyroid hormones, T3 (B) and T4 (C) were reduced by PTU exposure. T4 concentrations fell below the level of detection of the assay (nd < 2.5 ng/dl) on samples from PN3 and PN21. Upon termination of dosing on PN21, considerable recovery was evident by PN30. In a separate experiment with a regimen of PTU exposure that induced comparable reductions in body weight and thyroid hormones [43], complete recovery of thyroid hormone status was evident in adulthood (PN78 and PN200).

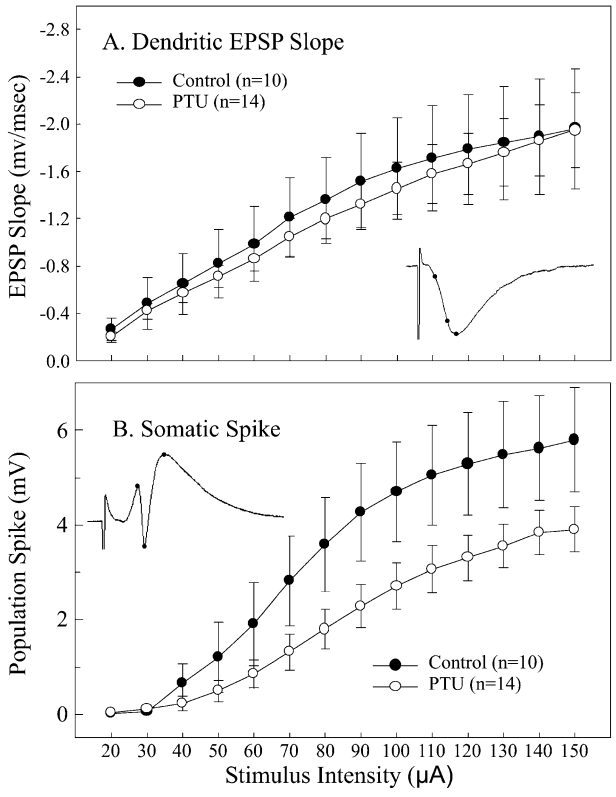

Fig. 2. Baseline synaptic transmission is impaired by PTU exposure. (A) Mean percent (± S.E.M.) EPSP slope was not different in slices taken from control and PTU-exposed animals. Inset shows a recording from the dendritic region and the points identified for scoring the EPSP slope and EPSP peak. (B) Mean percent (± S.E.M.) population spike amplitude was reduced in slices from PTU-exposed relative to control animals. Inset shows recording from the pyramidal cell layer and points identified for scoring the population spike.

magnitude of LTP. LTP was measured by comparing both the average EPSP slope and the population spike amplitude during the last 10 min of the pretrain recording period to that observed 10–30 min following delivery of the LTP-inducing trains. Only a single slice from any given animal was included in any one-dose group.

3. Results

Body weight decrements in PTU-treated offspring emerged by PN14 with severe reductions evident at weaning. Although significant catch up occurred upon cessation of treatment, differences between groups persisted into adulthood (Fig. 1A). Circulating thyroid hormones were suppressed when assessed on the final day of dosing (PN21). No change in T3 was apparent on PN3, but reductions of approximately 50% were evident on the final day of dosing (Fig. 1B). Serum levels of T4 were below the level of detection when initially assessed on PN3 and remained so until dosing was terminated on PN21 (Fig. 1C). Significant recovery had occurred by the time the pups were weaned on PN30, T3 was within 20% of control levels, whereas T4 remained ~ 40% below control levels. Thyroid hormone levels typically return to normal levels within a few weeks following cessation of PTU treatment [11,40]. Sawin et al. [40] report full recovery of thyroid hormones by PN35 following an identical developmental exposure protocol that included dosages of PTU in excess of those utilized in the present study. Unfortunately, blood samples at adult timepoints were not available for animals in the present study. However, recent data from our laboratory utilizing a developmental dosing protocol of longer duration (GD6–PN30) that produced comparable declines in body weight and hormone reduction [43], revealed complete recovery of thyroid hormones on PN78. These data are presented as adjuncts to Fig. 1B and C. Thus, it is reasonable to assume that the thyroid hormone status of animals in the present study was normal by the time testing began at 7 months of age.

3.1. Baseline synaptic transmission and paired pulse facilitation

Baseline synaptic transmission was reduced by perinatal hormone insufficiency as revealed by alterations in population spike amplitudes in baseline I/O functions. EPSP slope amplitudes were comparable between control and treated groups (Fig. 2A, $p>0.76$), but the population spike was significantly reduced in amplitude in the PTU-exposed group (Fig. 2B, Dose × Intensity $F(13,286)=2.38$, $p<0.005$).

Paired-pulse facilitation was evaluated at maximal and submaximal stimulus strengths over a range of interpulse

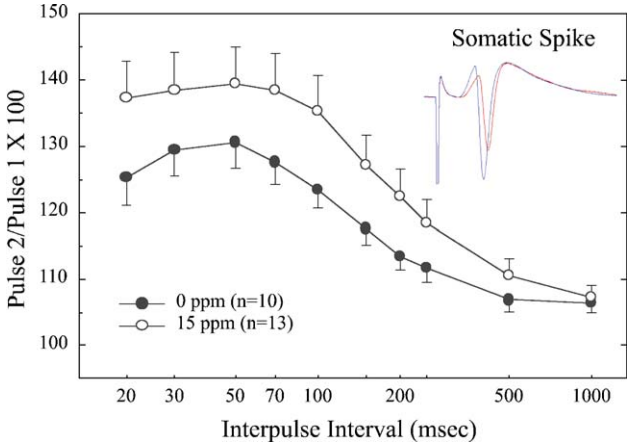

Fig. 3. Paired pulse tests at the somatic site are not changed by PTU exposure. Paired pulse facilitation of the population spike recorded from the pyramidal cell layer in area CA1 appeared to be enhanced in slices from PTU-exposed animals relative to controls, but this difference failed to reach statistically reliable levels ($p<0.07$). The degree of facilitation observed at the somatic level is modulated by synaptic inhibition, suggesting, at least for the brief IPIs, a trend towards reduced inhibitory function in PTU-exposed animals. Inset shows augmented population spike amplitude to the second pulse of the pair at an interval of 20 ms in a slice from a control animal. The data suggest that the degree of augmentation was exacerbated in slices from PTU-exposed animals.

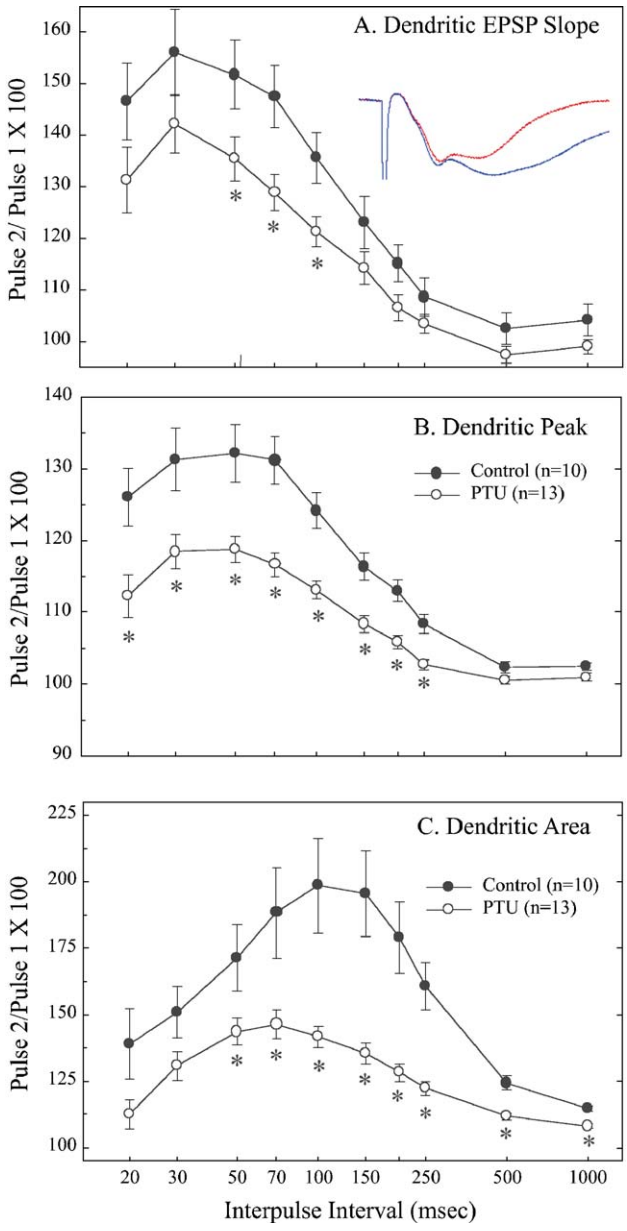

Fig. 4. Paired-pulse tests at the dendritic site are reduced by PTU exposure. Paired pulse facilitation was permanently reduced by developmental exposure to PTU in EPSP slope (A), EPSP peak (B), and EPSP area (C) estimates. These observations implicate perturbations in presynaptic transmitter release and GABA-mediated disinhibition as a function of transient developmental PTU exposure. Inset shows augmentation of the EPSP slope, peak amplitude, and area to the second pulse of the pair at a 200-ms interval.

intervals in both the dendritic and the somatic fields. Paired pulse facilitation of the population spike recorded from the cell soma layer appeared to be enhanced in PTU-exposed animals (Fig. 3), but results failed to reach statistically significant levels for maximal (Dose × Interval $F(9,189) = 1.80$, $p > 0.071$) or submaximal stimulus strengths (data not shown). In contrast, reductions in paired pulse facilitation were clearly evident in EPSP measures of slope, peak amplitude, and area. In slices from control animals, facilitation of the EPSP slope and peak was greatest at 30–50 ms, and then declined in magnitude as the interval between pulses increased (Fig. 4A and B). Little augmentation of the second pulse of the pair is evident at the longest intervals tested (i.e., paired pulse ratios are close to 100% at intervals of 500 and 1000 ms). In contrast to EPSP slope and peak measures, paired-pulse facilitation of the EPSP area were greatest at an interval of 100 ms, and facilitated responses were still evident at the longest interval tested (Fig. 4C). Short-term plasticity of all three measures of EPSP amplitude was markedly curtailed in slices from PTU-treated animals (Fig. 4). The maximal reduction in paired pulse facilitation of the EPSP slope (Dose $F(1,21) = 4.85$, $p < 0.0389$) and EPSP peak (Dose × Interval $F(9,189) = 74.37$, $p < 0.0001$) in slices from PTU-exposed animals occurred at intervals of 20–100 ms. Paired pulse facilitation of EPSP area was also significantly reduced in PTU-exposed animals with the greatest reductions evident at intervals of 70–250 ms [Dose × Interval $F(9,189) = 7.87$, $p < 0.001$). The data presented in Fig. 4 are the results from stimulation at a maximal intensity of 150 μA, and com-

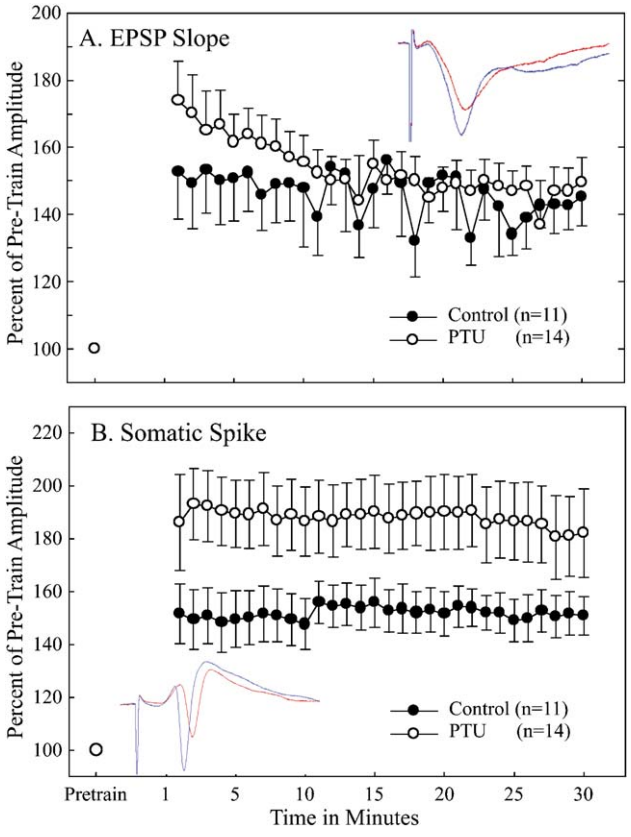

Fig. 5. Long-term potentiation is enhanced by PTU exposure. (A) EPSP slope was increased in slices from control and PTU-exposed animals and the magnitude of that increase was comparable between groups. In contrast, mean percent (± S.E.M.) change from pre-LTP baseline (Pretrain) response amplitudes of the population spike was augmented above control levels as a result of PTU exposure. Insets show representative tracing of EPSP (A) and population spike (B) amplitudes before and after train delivery.

parable results were obtained at moderate stimulus strengths (75–85 μA, data not shown).

3.2. Long-term potentiation (LTP)

Robust LTP of the EPSP slope and population spike was evident in slices from control and PTU-exposed animals (Fig. 5). Surprisingly, population spike LTP was enhanced in slices from PTU-exposed relative to control subjects throughout the 30 min posttrain recording period ($F(1,23) = 4.73$, $p < 0.04$; Fig. 5B). No effect of PTU was seen in LTP of the EPSP slope ($F(1,23) = 0.09$, $p > 0.76$; Fig. 5A).

4. Discussion

Thyroid hormone insufficiency beginning late in gestation and extending throughout lactation produced permanent alterations in synaptic transmission and plasticity in slices taken from adult animals. PTU possesses a very short half-life and following exposures of 1 month, thyroid hormones return to control levels within a few weeks [11,40]. Despite recovery of thyroid hormone status, population spike amplitude and short-term plasticity were reduced, whereas long-term synaptic plasticity as measured by LTP was augmented. As such, a subchronic period of perinatal hormone insufficiency was capable of permanently disrupting the fundamental properties of synaptic communication in this forebrain structure. To our knowledge, this is the first report describing permanent deficits in physiological properties of hippocampal area CA1 following perinatal thyroid hormone deprivation.

No significant alteration in baseline synaptic transmission was evident from I/O functions of EPSP slope (Fig. 2A) but population spike amplitudes were reduced in PTU-exposed animals (Fig. 2B). Reduced amplitudes recorded at the somatic level with no change in the dendritic synaptic response could reflect reduced cell excitability. Alternatively, extracellular population spike measures reflect the degree of synchrony of many very brief action potentials from multiple cells. A slight increase in asynchrony induced by PTU could lead to reductions in population spike amplitude. In contrast, in a recent study, increases in both measures of synaptic transmission were observed in area CA1 of animals exposed to PTU throughout gestation and lactation and tested just prior to weaning when thyroid hormones remained suppressed [43]. The role of thyroid hormones on nongenomic mechanisms that may acutely alter physiological responsiveness in area CA1 [15,25,39,44], the age of the animal at the time of testing, and the extensive prenatal exposure in the latter study (GD6–PN30) may contribute to the opposing effects on baseline measures of synaptic transmission.

Consistent with previous work, short-term plasticity in the form of paired pulse facilitation of the EPSP was profoundly disrupted in PTU-exposed animals [43,46]. Although both excitatory and inhibitory influences contribute to the absolute magnitude of paired pulse facilitation, presynaptic release mechanisms are primarily operative at intermediate interpulse intervals of 30–70 ms [12,36,48]. The maximal reduction in paired pulse facilitation of the EPSP slope and EPSP peak in slices from PTU-exposed animals included intervals within this time window, suggesting a primary effect of perinatal thyroid hormone insufficiency on mechanisms of transmitter release. In preweanling hypothyroid animals, Vara et al. [46] demonstrated that normal physiological function could be restored by T3 supplements administered 3 days prior to physiological assessment. The present study demonstrates, however, that the opportunity for rescue may be temporary as return of thyroid hormone concentrations to the normal range when treatment was terminated was insufficient to compensate for deficits induced by transient perinatal hypothyroidism.

In addition to presynaptic mechanisms that promote augmented responses to the second pulse of the pair, components of paired-pulse facilitation of the EPSP are also derived from disinhibition of GABA-mediated inhibitory postsynaptic potentials [2,3,14,32,36]. The pattern of paired pulse facilitation of EPSP area is distinct from that observed for EPSP slope and peak measurements in that the greatest facilitation of EPSP area is temporally shifted to longer intervals of 70–200 ms, presumably reflecting the predominance of disinhibition mechanisms in this parameter (compare Fig. 4A and B with C). Facilitation results from activation of presynaptic $GABA_B$ autoreceptors located on interneurons that serve to limit further release of inhibitory transmitter and permit activation of depolarization-dependent *N*-methyl-D-aspartate receptors [32,35]. As with EPSP slope and peak amplitudes, paired-pulse facilitation of the EPSP area was also profoundly suppressed by transient thyroid hormone insufficiency during development.

In contrast, paired pulse measures of the population spike demonstrated a trend towards augmentation in slices from PTU-exposed animals and corroborate previous work in weanling-aged hypothyroid animals [43]. Augmentations in facilitation of the population spike are typically interpreted as reductions in GABAergic inhibitory tone [33,36].

A number of similarities are evident between the effects of developmental hypothyroidism on synaptic function in the CA1 and dentate subregions of the hippocampal formation. Littermates of animals from the current study exhibited profound reductions in baseline synaptic transmission of the EPSP slope and population spike in the dentate gyrus [19]. A milder impact of hypothyroidism on baseline synaptic transmission in area CA1 may derive from the relative maturity of these two subregions at the time of hormone deprivation [4,26,28,37,38]. In the dentate gyrus, hormone insufficiency was induced by the current dosing regimen during the period of peak neurogenesis, cell migration and active synaptogenesis. Exposure beginning in the late ges-

tational period falls outside the window of these events in the primarily prenatal development of area CA1. In addition, there is also evidence for selective vulnerability in dentate gyrus relative to area CA1 in the expression of protein substrates critical for synaptic transmission and plasticity [22,24].

LTP was also assessed in the dentate gyrus by Gilbert and Paczkowski [19] where reductions in EPSP slope LTP were observed in conjunction with augmentations in population spike LTP. Consistent with a less severe impact of hypothyroidism in area CA1, no effects of EPSP slope LTP were evident in CA1 slices from hypothyroid animals in the present study. However, as in the dentate gyrus, a paradoxical enhancement of population spike LTP was observed. The mechanisms of hypothyroid-induced dissociation of dendritic and somatic indices of synaptic plasticity are unknown. Subtle changes in synaptic structure can alter the biophysical properties of synapses and have profound effects on synaptic transmission and plasticity [16,23]. Ultrastructural changes at the synaptic level have been documented in all three subregions of the hippocampal formation of hypothyroid animals [26–28,37,38]. In the present study, increases in the magnitude of population spike LTP could reflect PTU-induced structural abnormalities that perturb cell excitability in the absence of altered synaptic input. Disproportionate augmentations in somatic relative to dendritic indices of LTP can be induced acutely by reducing intracellular calcium, metabotropic glutamate receptor activation, and GABA-mediated inhibition [8,17,45]. Perturbations in presynaptic calcium function are suggested by the diminution of paired pulse facilitation so prevalent in area CA1 of PTU-treated animals (i.e., present report, Refs. [43,46]). Potential compromise of GABA-mediated inhibition in area CA1 of the hypothyroid animal has been suggested (present study and Ref. [43]), and preliminary findings are indicative of impairment in the dentate gyrus of PTU-exposed animals [20]. Thus, enhancements in population spike LTP in area CA1 and dentate gyrus may culminate from hypothyroid-induced changes in synaptic structure, cellular excitability, presynaptic calcium function, or GABA-mediated inhibition.

Reductions in hippocampal concentrations of glia acidic fibrillary protein (GFAP), a marker for glial cells, are also seen in models of developmental hypothyroidism [29,37]. Although glia are not directly involved in electrical signaling in the nervous system, they serve to regulate synaptic activities by taking up neurotransmitters, buffering cations and pH, and presenting barriers for calcium diffusion [23]. During development radial glial cells also serve to guide migrating neurons and direct outgrowth of axons [30]. Consistent with observations in PTU-exposed animals, hippocampal slices from GFAP knockout mice exhibit increases in population spike LTP [30] suggesting that disruption of glial cells may represent a potential target contributing to the augmentation of somatic indices of long-term synaptic plasticity.

In summary, we have demonstrated permanent alterations in synaptic function of the hippocampus in adult animals undergoing a period of hypothyroidism throughout early postnatal life. Disruption of the thyroid axis was evident shortly after birth and persisted until after animals were weaned on PN30. A number of thyroid-responsive genes have been identified that are critical for cell migration, dendritic arborization, synapse formation, and myelination [5] and structural changes within CA1 pyramidal cells following perinatal hypothyroidism have been well documented. The present study indicates that these structural abnormalities are associated with functional deficits in hippocampal synaptic circuitry and together with previous findings, both CA1 and dentate gyrus subregions of the hippocampal formation are implicated in this dysfunction [19,34,43,46]. Deficits in short-term and long-term synaptic plasticity have been associated with impairments on a variety of cognitive tasks [6,10,31,42]. As the hippocampus represents a critical neural substrate for some forms of learning, compromises in hippocampal synaptic function and plasticity may contribute to cognitive impairments that accompany early thyroid hormone insufficiency [1,9,13,41].

Acknowledgements

The authors thank Drs. Tim Shafer, Steve Lasley and Li Sui for their thoughtful comments on an earlier version of this manuscript. Software development for data acquisition and analysis was performed by Dr. Joseph Ali and Malek Khan, Neurotoxicology Division, US EPA. Dr. Mark Stanton and Christine Paczkowski were instrumental in the initiation of this work and the technical assistance of Bill Anderson is gratefully acknowledged.

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