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Neonatal hyperthyroidism disrupts hippocampal LTP and spatial learning

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Summary. Excess thyroid hormone at an early stage of development produces marked neurochemical and morphological alterations in the rat hippocampal formation. In order to better understand the functional significance of these changes, we tested adult rats treated neonatally with triiodothyronine (T3), and their control litter mates, in a spatial learning task and for the induction of long-term potentiation (LTP) in the dentate gyrus (DG) of the hippocampal formation. The T3-treated rats were significantly impaired in their performance on the spatial task in comparison to their matched controls. Similarly, the efficacy of LTP induction was significantly attenuated in the T3-treated animals. Further, a significant correlation was obtained between LTP induction and performance on the spatial learning task. Thus, a brief neonatal excess of thyroid hormone produces impairments in spatial learning along with decreases in LTP, long held as a model of learning and memory. This relationship provides a unique opportunity to study associations between behavioral, physiological, pharmacological and morphological processes intimately associated with the hippocampal formation

Key words: Thyroid hormone – Development – Hippocampus – Dentate gyrus – LTP – Learning – Memory – Rat

Introduction

The late ontogenesis of the rodent hippocampal formation allows relatively simple experimental manipulations, carried out within the first few postnatal weeks, to interfere with neuronal (cell acquisition, migration and differentiation) and glial cell development in the hippocampus. For example, neonatal thyroid hormone (TH) administration produces morphological (Gould et al. 1990; Lauder and Mugnaini 1980; Rabie et al. 1979; Rami et al. 1986ab; Westlind-Danielsson et al. 1990) and neurochemical (Meaney et al. 1987; Rabie et al. 1979; Westlind-Danielsson et al. 1990) aberrations in the hippocampus which are detectable in the adult animal. There is a scarcity of studies, however, investigating the functional significance of these alterations. The hippocampus and closely related structures are believed to play a crucial role in learning and memory processes (Squire 1986). Using simple learning paradigms (i.e., conditioned avoidance, closed field test, Lashley-III maze and Y Water maze), a number of studies have reported that hyperthyroidism disrupts learning and memory in these tasks (Davenport et al. 1975; Eayrs 1964; Lipp et al. 1984; Lipp et al. 1988; Schapiro 1968). Recent theories of hippocampal function have stressed the role of this structure in spatial learning and memory (O'Keefe and Nadel 1978; Olton and Papas 1979). In the present study, rats neonatally treated with TH were tested on a spatial discrimination task. In addition, long-term potentiation (LTP), in the dentate gyrus of the hippocampus, was studied in these animals. LTP is characterized by an increase in synaptic efficacy following brief high frequency stimulation of afferent fibers and has been postulated as a model of neuronal plasticity. In the present study we demonstrated the deleterious effects of brief neonatal triidothyronine (T3) treatment on both the spatial learning and memory task as well as the efficacy of LTP induction.

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Material and Methods

Thyroid hormone administration

Twenty two newborn male and 12 female Sprague-Dawley rats (Charles River Labs) pooled from 9-11 dams were randomly assigned to each dam. The pups from each litter were injected either with a dose of 3,5,3′-triiodo- L- thyronine (T3) (0.5 μg/g body weight in 25 μl sesame oil, s.c., on P1, P2 and P4) or received the vehicle. Following weaning (P26), all rats were housed in groups of 3 and given water and Purina lab chow ad libitum. The animals were then allowed to mature to approximately 2-3 months of age.

At the conclusion of electrophysiological testing, the animals were sacrificed (under urethane anesthesia) and blood samples were collected for analysis of T3 and T4 serum levels. The adrenal glands were also removed and weighed.

Behavioral training

A subgroup of the adult male rats (8 T3 and 8 age-matched controls) were tested on a spatial learning task. The training was performed on an 8-arm radial maze, which was placed within a room 2.05 × 2.65 m. in diameter and which contained several well structured, constant extramaze cues. The arms of the maze (9 × 61 cm) radiated out at equal angles from a central platform (34 cm in diameter). The rats started from the central platform and could travel from one arm to another only by crossing the platform. Baits (two 45 mg NOYES rodent diet precision pellets) were placed in holes (2 cm wide × 0.5 cm deep) at the distal end of the arms. This made the food invisible to the animal from a distance; two of the arms were always unbaited. Unbaited arms were always the same for all test trials for a given rat but varied randomly across rats. Each time a rat entered halfway through one of the two always empty arms it was assigned a long term spatial learning error. Re-entering a baited arm halfway gave a short term learning error. Before testing, all rats were placed on a food deprivation schedule so that their body weight was kept at about 85% of normal. 3-5 rats were then placed together on the maze for 15 min to familiarize them with the maze and to assure that they knew the existence of the baits at the end of the arms before testing took place. Test order was randomized among rats and across days. Testing was terminated when a rat had eaten all six baits.

The experimenter was "blind" with respect to experimental and control group. At the commencement of testing, half of the rats were 50 days of age, whereas the other half were 81 days old. However, since it was later determined that age at time of testing had no influence on spatial performance, all data were pooled.

Electrophysiology

Following the behavioral testing all of these animals, including 3 supplemental pairs, were tested for hippocampal LTP. In addition, 7 T3 treated females and 5 matched controls were also tested for LTP. The results of the female rats will be presented separately.

The animals were anesthetized with urethane (1.7 g/kg, i.p.) and stereotaxically implanted with a recording electrode aimed at the granule cell (GC) layer of the dentate gyrus (DG) and a stimulating electrode aimed at the perforant path (PP). (For detailed recording, stimulation and data analysis methods see Greenstein et al. 1988). The experimental paradigm consisted of first adjusting the stimulating and recording electrodes to produce maximum field responses (see Fig. 2a inset for a representative field response). A test stimulus (0.25 ms pulse-width) was then selected that would elicit a small population spike (1-2 mV; approximately 1/3 of saturation current). Both the slope of the population EPSP and the amplitude of the population spike were calculated on-line and displayed graphically to ascertain the induction of LTP (Stromquist et al. 1990). Testing for this part of the study was also performed "blind" in terms of T3 and control group.

A baseline was then obtained by delivering a pulse (0.25 ms pulse width) to the PP every 30 seconds for 15 min, and recording the field potentials (average of 3 responses, 1/5 s). Following baseline recordings, brief tetanic stimulation, at an intensity level sufficient to induce a minimum spike, was delivered to the PP (10 pulses, 200 Hz, 5 times, 10 s apart) and the field responses were once again calculated for 20 min. The intensity of the tetanic stimulation was then increased to a level approximately 40% of saturation and the procedure was repeated. Tetanization at this second, higher stimulus intensity was performed to ensure that the responses were not saturated following the first tetanus.

Results

Thyroid hormone

The thyroid hormone treatment produced classical signs of neonatal hyperthyroidism—eyes opened 2-3 days earlier (approx. P11) than the controls and locomotor activity increased, in agreement with previously published results (Schapiro 1968; Westlind-Danielsson et al. 1990). The body weights of each T3 rat was consistently lower (approx. 13%) when compared to its experimental control. The adrenal weights of the T3 animals (X = 43.2 mg ± 1.6 SEM) were also significantly lower than those of the controls (X = 68.0 mg ± 5.2 SEM, $p < 0.001$; unpaired two-tailed student's t-test). This corroborates earlier findings (Evans et al. 1964; Bakke et al. 1975; Westlind-Danielsson et al. 1990). Finally, at time of study, the T3 rats were considered euthyroid with respect to serum levels of T3 [controls ($n = 3$) X = 31.0 ng/dl ± 4.4 SEM: T3 ($n = 6$) X = 30.3 ng/dl ± 12.6 SEM] and T4 [controls ($n = 3$) 2.4 ng/dl ± 0.6 SEM: T3 ($n = 6$) 1.7 ng/dl ± 0.3 SEM].

Behavior

The behavioral data were analyzed for the number of arms chosen before committing the first short term error, the number of short and long term errors, and the total time and number of arms visited in order to eat all 6 baits. To test for significant differences in behavior, a repeated MANOVA was used in which treatment constituted one factor and training (6 successive blocks (three trials each) on consecutive days) was the other factor. Adult short-term spatial learning capacity was significantly reduced in the T3 rats [$F(1, 12) = 6.7$, $p < 0.05$] (Fig. 1A). (In this and the following analysis, training effects reached significance at $p < 0.001$, whereas, treatment × training interactions were not significant.) Thus, at each block of trials the control animals performed significantly better than the T3 animals. Further, although the T3 animals appear to improve with each block of trials they did not reach criterion even after extensive training. It should be noted that the initial difference in performance between the control and T3 animals (Fig. 1A) is probably due to rapid improvements in spatial memory by the control rats even within a block of trials (each block represents an average of 3 trials).

In contrast to the working-memory deficit, long-term spatial learning was not affected by the T3 treatment [$F(1, 12) = 2.6$, $p = 0.13$]. Most T3 rats needed more time to complete the task than did the controls [$F(1, 12) = 13.2$, $p < 0.005$] (Fig. 1B). In order to distinguish a performance from a learning deficit we developed an overall time-error spatial learning index by adding total time (in minutes) to the number of the two types of errors. T3 rats obtained a significantly higher time-error index than the controls [$F(1, 12) = 10.13$, $p = 0.008$] (Fig. 1C). Moreover, T3 rats needed more visits to reach all baits [$F(1, 12) = 7.8$, $p = 0.016$] but the number of choices made before committing an error did not differ between groups [$F(1, 12) = 2.3$, $p = 0.06$]. In all, it would be safe to characterize this as

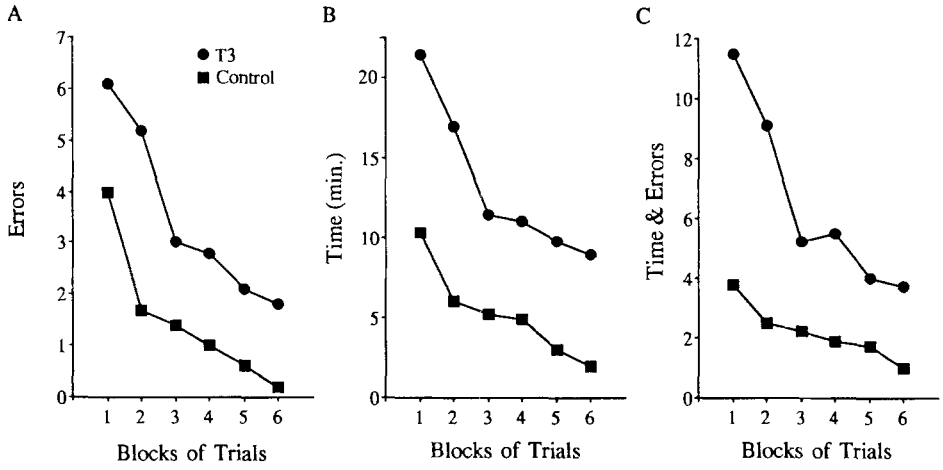

Fig. 1A–C. Evidence for suppressed spatial learning capacity in T3 and control rats. (**A**) Short-term spatial learning error. (**B**) Time to complete entire task. (**C**) Overall time plus short- and long-term errors index. All data are for male animals 50–98 days of age. Groups differed significantly at $p=0.024$, 0.003 and 0.008, respectively. Note that the T3 animals learn at a significantly lower rate and they also don't reach criterion even at the last day of training

a learning and memory deficit as opposed to a decline in performance.

Electrophysiology

Male animals. The effects of tetanic stimulation were calculated as percent change from previous condition (i.e. TET I in comparison to baseline and TET II in comparison to TET I). (Although post-tetanic potentiation (PTP) was observed in a number of animals its duration was short lived (in most cases less than 3 min) and it did not occur in all cases. Percent changes were, therefore, calculated over all responses within a condition.) Analysis of the population spike revealed that in 10 of the 11 control animals a significant (T-test, $p<0.001$) degree of potentiation in comparison to baseline was induced following the first tetanization (TET I) (see Figs. 2 and 3A for an example). The mean potentiation ($\pm$SEM) for the control group as a whole was 86.6% ($\pm$26.6%). In contrast, 5 of the 11 T3 animals showed a significant degree of long-term depression (LTD) in comparison to baseline (see Fig. 2 and 3B for an example). Only five T3 animals produced a significant degree of potentiation. The mean potentiation of all of the T3 animals was 3.5% ($\pm$16.9%). ANOVA for percent potentiation revealed significant differences between the control and the T3 groups [$F(1, 20)=6.97$, $p<0.05$] (Fig. 4). Tetanization at a higher stimulus intensity (TET II) produced further significant (T-test, $p<0.001$) increases in 7 of the 10 control animals tested. The mean potentiation ($\pm$SEM) (in comparison to TET I) for the control group as a whole was 58.04% ($\pm$16.3%). Similar tetanization (TET II) in the T3 group produced significant increases in 7 of the 9 animals tested. The mean potentiation (in comparison to TET I) for the T3 group was 43.9% ($\pm$9.9%) (Fig. 4).

In terms of the EPSP slope, 8 of the control animals showed a significant increase (T-test, $p<0.001$) following the first tetanus (TET I) while the slope of the remaining 3 animals did not change. The average change of the EPSP slope for the entire control group was 13.0% ($\pm$2.0%). In comparison, the EPSP slope of 5 of the T3 animals increased significantly while 3 animals showed a significant decrease (Fig. 4). The average change for the

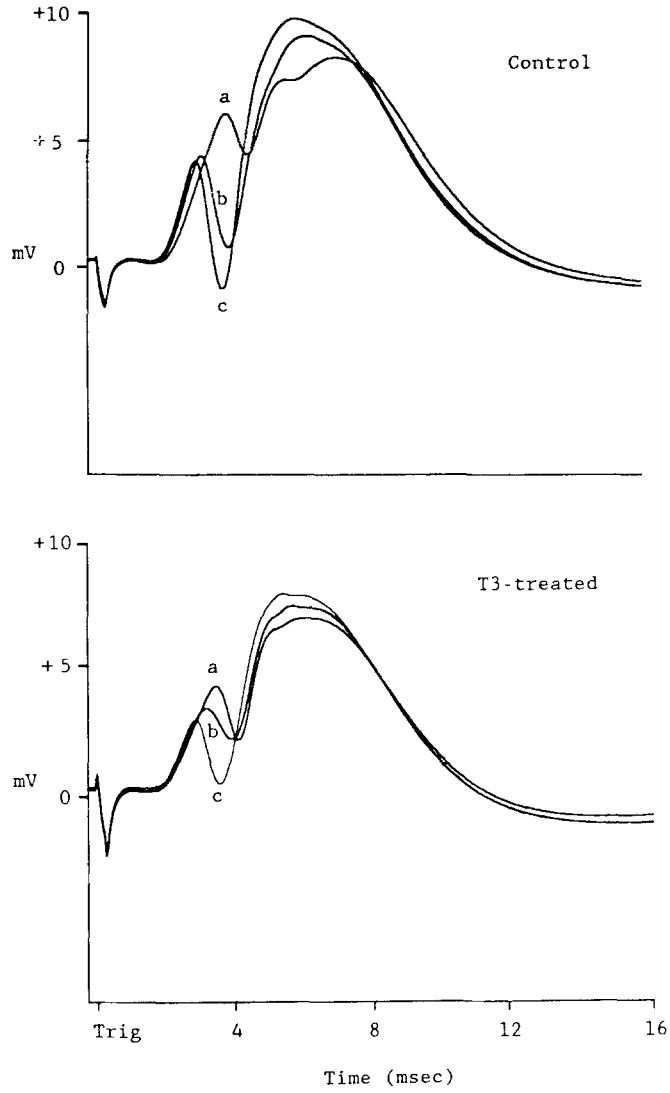

Fig. 2. Effects of tetanic stimulation on field potentials recorded in the dentate gyrus granule cell layer with stimulation applied to the perforant path, in control and T3-treated animals. Each of the field potentials represent averages of 3 responses. Trace *a* was recorded during baseline while traces *b* and *c* were recorded following TET I and TET II respectively. Field potentials were obtained from subjects presented in Fig. 3

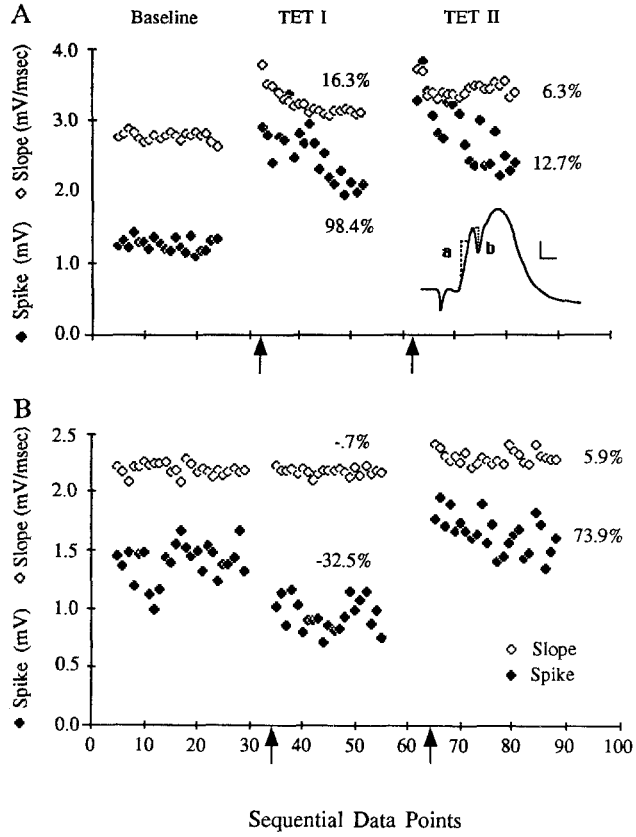

Fig. 3A, B. Representative example of tetanization effects on the EPSP slope (open diamond) and spike (black diamond) in control (**A**) and T3 (**B**) animals. For the control animal, initial tetanization (TET I) produced a significant degree of potentiation as evidenced by an increase of both the EPSP slope and population spike. A second tetanization (TET II), at a higher stimulus intensity, produced a further degree of potentiation. In contrast, the initial tetanization in the T3 animal did not produce a significant change for the EPSP slope and produced a marked depression in the population spike. Tetanization at a higher intensity, however, produced significant increases in both the EPSP slope and spike. Percent changes were calculated from previous condition. Each point is an average of 3 responses and were obtained at 1 minute intervals. The arrows indicate the time at tetanization. Inset illustrates a representative field response: EPSP slope (*a*) and population spike (*b*) were calculated on line. Calibrations: 2 mV and 2 ms, positivity upward

entire T3 group was 1.4% (±4.1%). ANOVA for the percent change in EPSP slope between the control and T3 animals revealed significant differences [$F(1,20)=6.45$, $p<0.05$]. Tetanization at the higher intensity (TET II) produced further changes in the slope of the EPSP. The slope of the control group increased by 6.7% (±2.1%) (in comparison to TET I) while the slope of the T3 group increased by 2.1% (±2.2%) (Fig. 4).

Overall correlations performed between the time-error index obtained in the spatial learning task and the degree of LTP induced in the DG revealed a negative correlation for the population spike ($r=-0.50$, $p<0.05$) and the EPSP slope ($r=-0.35$, $p=0.09$). Thus, judging from the population spike the lower the score obtained on the spatial task (i.e., fewer errors) the higher the degree of potentiation.

Female animals. The mean potentiation (±SEM) from baseline for the population spike of the control animals following the initial tetanus (TET I) was 145.73% (±26.56%). In contrast, similar tetanization in the T3 animals produced 49.6% (±16.01%) potentiation from baseline. ANOVA between the control and T3 animals revealed significant differences [$F(1,11)=7.93$, $p<0.01$]. Tetanization at a higher intensity (TET II) produced a further (30% ± 8%, NS) increase for control animals with a much larger (88.13% ± 20.80%) [$F(1,1\text{ɔ})=11.83$, $p<0.005$] increase for the T3 animals (Fig. 5). In contrast to the male animals, in none of the female T3 animals was a long-term depression effect observed, following high frequency stimulation.

In contrast to the population spike (and the results obtained with the male rats), high frequency stimulation (TET I) produced comparable changes in the EPSP slope between the control (18.40% ± 5.0%) and T3 (17.28% ± 2.49%) animals. Tetanization at the higher intensity (TET II) produced further, although not significant, increases to the EPSP slope (Fig. 5).

Discussion

Early treatment with thyroid hormones is known to cause accelerated development in rats; thus behaviorally, pre-

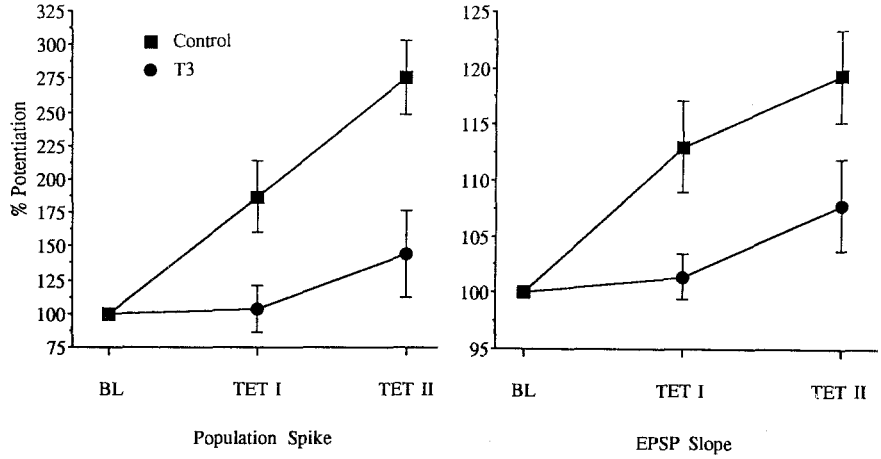

Fig. 4. Effect of tetanic stimulation applied to the perforant path on the population spike and EPSP slope recorded in the dentate gyrus granule cell layer, for the *male* animals. Shown are the average percent changes (±SEM) from baseline (BL) following the initial tetanization (TET I) and following a second, higher intensity tetanus (TET II). It should be noted that the potentiation produced by the second tetanus was in addition to that produced by the first (i.e., percent change is calculated from previous condition)

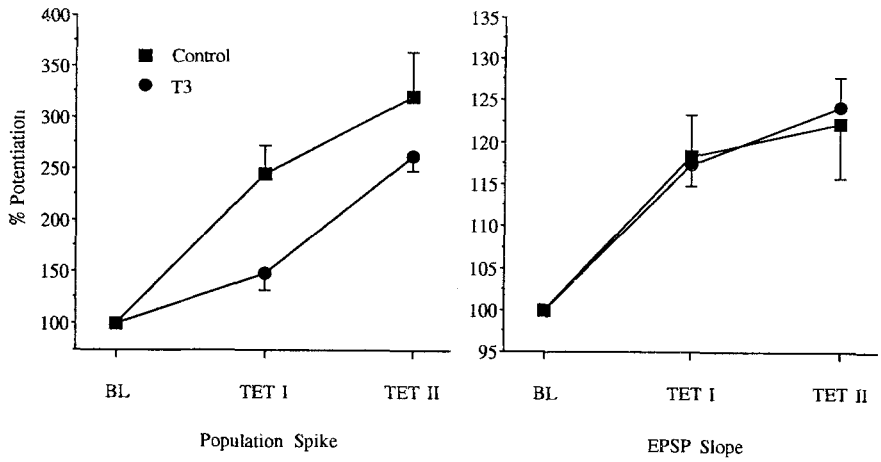

Fig. 5. Effect of tetanization on the population spike and EPSP slope for the *female* animals. Shown are the average percent changes (±SEM) from baseline following TET I and following a second, higher intensity tetanus (TET II)

pubertal rats show advanced learning abilities (Schapiro 1968; Schapiro et al. 1970). However, the advantages of these precocious developmental effects are not maintained throughout life. On the contrary, adult rats neonatally administered excess thyroid hormone perform significantly worse than control rats on a number of simple behavioral tasks (Eayrs 1964; Schapiro 1968) as well as in a two way-avoidance task (Lipp et al. 1988). Our behavioral results with adult rats agree with the findings from these studies and extend the observations to include deficits of T3 treated rats in spatial learning and memory tasks.

The correlation between LTP and performance on the spatial learning and memory task is of great interest. Although the correlation does not show a direct link between LTP and behavior, it nonetheless demonstrates that treatments producing a deficits in the former also produce deficits in the latter.

Of interest is also the LTD observed in the T3 animals. Homosynaptic depression of DG granule cell EPSP's following brief, high frequency stimulation of the PP has not previously been reported. (However, using either low frequency stimulation or very long trains of high frequency stimulation, it has recently been shown (Bramham and Srebro 1987) that LTD can also be induced homosynaptically in the DG granule cells.) A plausible explanation for the LTD is that it reflects an increase in inhibitory processes following high frequency stimulation. Inhibitory processes have been shown to modulate LTP induction (Douglas et al. 1982; Wigstrom and Gustafsson 1983). An increase in gamma aminobutyric acid (GABA) has been reported in hippocampal slices made epileptogenic with entorhinal cortex stimulation (Leibowitz et al. 1978). A similar increase in GABA may also occur with short tetanic stimulation as a result of the T3 treatment. The axon collaterals of the DG granule cells have recently been shown to be rather extensive (Claiborne et al. 1986). These fibers terminate on GABAergic basket cells (Ribak and Seress 1983), which in turn mediate inhibitory influences on the granule cell bodies (Andersen 1975). Neonatal TH administration produces a drastic and aberrant growth in the mossy fibers (Lauder and Mugnaini, 1977; 1980; Represa et al. 1987) which develop postnatally. If the thyroid hormone induced hyperplasia of the mossy fibers also involves this collateral plexus, a stronger inhibitory influence on the granule cells may ensue following high frequency stimulation, which could increase the efficacy not only of excitation but also of feedback inhibition (Kairis et al. 1987). Consequently, a higher intensity tetanic stimulation for LTP induction in the T3 rats would be required to overcome the increased inhibition produced by an increased volume of the mossy fiber-collateral plexus. Indeed, increasing the intensity of the tetanic stimulation in the present experiments (TET II) produced significant increases in the both the EPSP slope and population spike of the T3 animals. It is also possible, however, that changes in membrane conductance, transmitter depletion, receptor distribution or desensitization, among other mechanisms, could also explain the observed LTD. Elucidation of the mechanaisms underlying LTD await further anatomical and pharmacological analysis. Regardless of the mechanisms, the implications of this finding are substantial. The DG granule cells are a critical relay of information (arising from the entorhinal cortex) through the hippocampal formation. Information flow through the DG granule cells can be gated or restricted under certain physiological conditions (Winson and Abzug 1978). Restriction or disruption of information flow through this structure, via some inhibitory mechanism (i.e., LTD), may offer an explanation for the observed behavioral deficit.

A number of electrophysiological differences were observed between the male and female animals. For example, while the population spike of the female control animals increased significantly in comparison to the T3 animals, no significant changes were observed for the EPSP slope between the control and T3 female rats. Further, in no case was a long-term depression observed for the female animals. The sex-linked differences in electrophysiology may reflect differential thyroid hormone effects on the anatomy of the dentate gyrus. Thus, the T3 treatment may have affected the female rats to a lesser extent than the male animals. Developmental sex-linked differences in the anatomy and possible effects on behavior will have to be further investigated.

The late ontogenesis of the rodent hippocampus creates a particularly favorable target region for the action of thyroid hormones (Patel and Balazs 1980) with respect to

their ability to remodel the morphological framework for neuronal circuitry in neonatal rats (Gould, Westlind-Danielsson et al. 1990; Lauder and Mugnaini 1977; Westlind-Danielsson, Gould et al. 1990). We have found that early thyroid hormone treatment leads to significant attenuation in LTP induction as well as a deficit in learning and short-term memory processes. This provides a unique opportunity to study possible relationships between behavioral, physiological, pharmacological and morphological processes intimately associated with the hippocampal formation.

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