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Early postnatal decabromodiphenyl ether exposure reduces thyroid hormone and astrocyte density in the juvenile mouse dentate gyrus

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ABSTRACT

Decabromodiphenyl ether (decaBDE) is a flame retardant that was widely-applied to many consumer products for decades. Consequently, decaBDE and other members of its class have become globally-distributed environmental contaminants. Epidemiological and animal studies indicate that decaBDE exposure during critical periods of brain development produces long-term behavioral impairments. The current study was designed to identify potential neuroendocrine mechanisms for learning and response inhibition deficits observed by our lab in a previous study. C57BL6/J mouse pups were given a single daily oral dose of 0 or 20 mg/kg decaBDE from day 1 to 21. Serum thyroid hormone levels and astrocyte-specific staining in three regions of the hippocampus were measured on day 22. DecaBDE exposure significantly reduced serum triiodothyronine, thyroxine, and astrocyte density in the subgranular zone but not the hilus or granular layer in both male and female mice. The reduction of thyroid hormone and/or glia activity could impair hippocampal development, leading to behavior dysfunction.

1. Introduction

Decabromodiphenyl ether (decaBDE) and other polybrominated diphenyl ethers (PBDEs) are flame retardant chemicals that are used to protect household objects such as electronic equipment and textiles in furniture and mattresses. Point source releases and atmospheric fallout of decaBDE have contaminated water sources [52,34]. DecaBDE has also entered the food web. It is found in fish, meat, cheese, breast milk, and sewage sludge [13,33,37,38]. DecaBDE is also a major contaminant in clothes dryer lint and dust collected from homes and cars. Dust ingestion is likely a major route of exposure for infants and toddlers due to their increased hand-to-mouth behavior [5, 30, 40].

In the United States, the production of two other PBDE congeners, penta- and octaBDE, was voluntarily withdrawn after their sale was banned by the European Union. In 2008, the European Union also banned decaBDE, which was followed by a voluntary phase-out in the United States. However decaBDE continues to be sold in developing countries. In more recent studies, decaBDE was the dominant congener in human breast milk samples collected in China [39] and several urban centers in India [6].

A number of PBDE congeners have been shown to produce learning and memory deficits in laboratory animals when exposure occurs during critical periods of brain development [2,42,46,51]. In mice, decaBDE exposure leads to habituation failure, impaired acquisition in the Morris Water Maze, and impaired response inhibition during operant responding [47,21,3,22,28]. A negative correlation between decaBDE levels in colostrum and mental development in infants has also been observed [9]. Some of these behavioral effects could be the consequence of a decaBDE-mediated disruption of the thyroid hormone system. Adequate circulating thyroid hormone during critical periods of development is important for healthy brain, muscle, bone, and reproductive development. Children living near electronic waste facilities have elevated blood PBDE levels, elevated thyroid stimulating hormone, and lowered triiodothyronine (T3) and thyroxine (T4) [50]. PBDEs are believed to mimic the chemical structure of the T4 and compete for binding to the T4 transport protein, resulting in disrupted transport and circulation [15,23,27,53]. In mice, developmental exposure to decaBDE has been shown to either reduce [8,32,44] or increase circulating levels of thyroid hormone [28], reduce expression of thyroid hormone receptors [36], and alter the iodothyronine deiodinases that regulate thyroid hormone homeostasis in the brain [28].

Thyroid hormone plays a critical role in glial proliferation and

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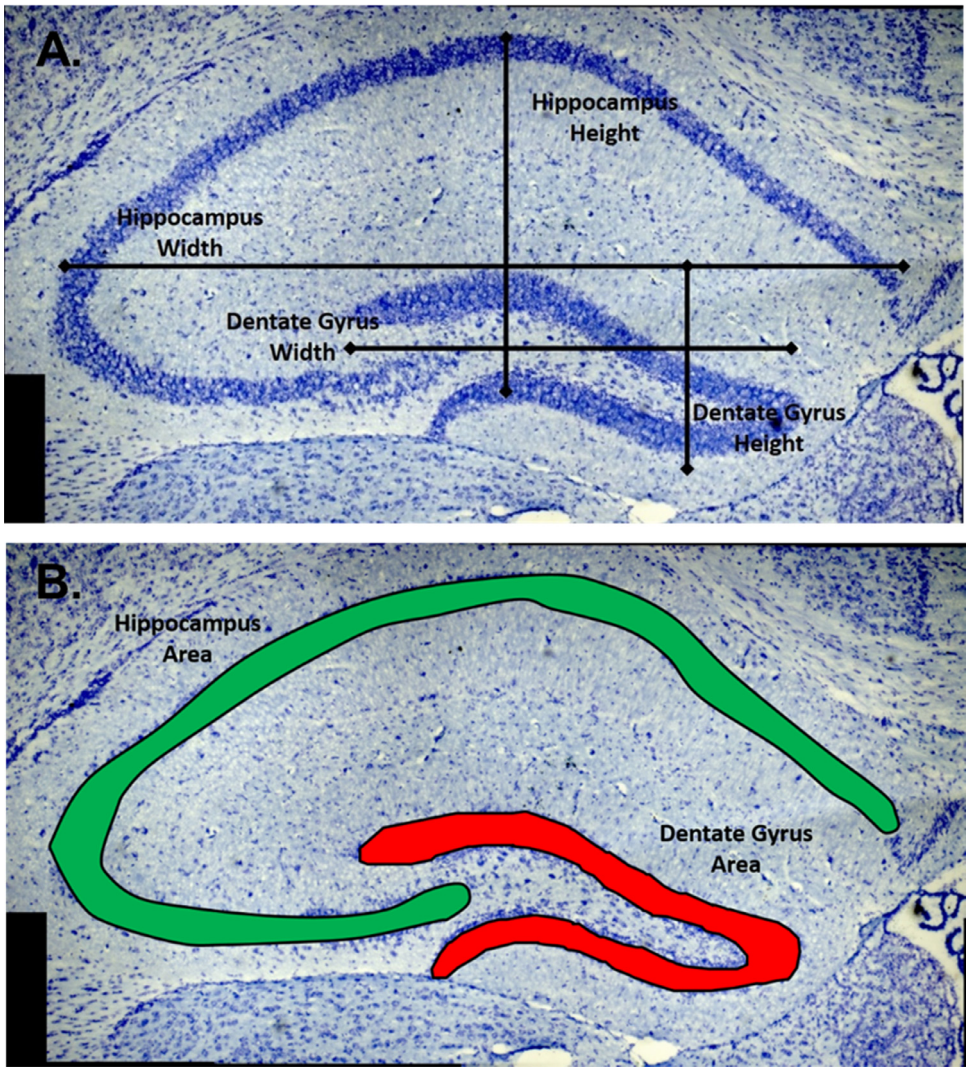

Fig. 1. The linear measurements (A.) and area measurements (B.) collected in the cresyl violet-stained sections of the hippocampus in 22-day old mice.

differentiation in the developing brain [12]. Astrocytes in turn mediate the effects of thyroid hormone on neuronal proliferation, migration, differentiation and axonal growth [7,43]. Astrocytes might serve to protect PBDE-exposed neurons by lowering oxidative stress [10]. The relationship between astrocytes and thyroid hormone suggests that the observed decrease in thyroid hormone following decaBDE exposure could be accompanied by a deficit in astrocytes. In support of this theory, the commercial PBDE mixture, DE71 has been shown to trigger apoptosis of both neurons and astrocytes in cell cultures harvested from neonatal mice [11].

One brain structure where PBDE-initiated cell death has been observed is the hippocampus [21,41,51]. A large body of evidence describes the cause-effect relationships that link the key developmental events of decreased serum T4, to decreased neuronal T4, followed by altered hippocampal gene expression, and resultant altered hippocampal anatomy [24]. A particularly sensitive region might be the dentate gyrus because it promotes neurogenesis throughout the lifespan. Since some astrocytes that arise from the stem cell niche in the subgranular zone (SGZ) differentiate into granule cells, a direct impact on glia cells could further alter the neuronal population of the dentate gyrus [4,17]. Because the development of the mouse dentate gyrus is largely postnatal, the current study was designed to assess serum thyroid hormone levels and astrocytic density in the mouse hippocampus following early postnatal exposure to decaBDE. Mice used in the current study were littermates of those that were examined in a larger behavioral study [22]. That study revealed a range of persisting motor deficits and impaired response inhibition in a differential reinforcement of low rates (DRL) operant procedure following exposure to 20 mg/kg decaBDE from postnatal day 1–21. The effects on response inhibition again suggest that development of the hippocampus might have been disrupted by decaBDE since hippocampal lesions have previously been shown to impair DRL performance in mice [31].

2. Materials and methods

2.1. Breeding and decaBDE exposure

Adult male and female C57BL/6 J inbred mice (The Jackson Laboratory, Bar Harbor, ME) were housed in vivarium quarters at the State University of New York at Geneseo, fed standard pellet chow (LabDiet 5001, Brentwood, MO) ad libitum, and were maintained on a reversed 12-hr light:12-hr dark cycle in a room with an ambient temperature of 20 ± 2 °C and 40–60% humidity.

During the breeding period, females were examined every morning for the presence of a sperm plug. The day of birth was considered postnatal day (PND) 0 and litters were culled to 3 male and 3 female pups on PND1. Litters with fewer than 6 pups or a skewed sex distribution were not used. From PND1-21, each pup was administered a single oral dose per day of 0 or 20 mg decaBDE/kg bodyweight (product 194425, 98% 2,2′,3,3′,4,4′,5,5′,6,6′-decabromodiphenyl ether,

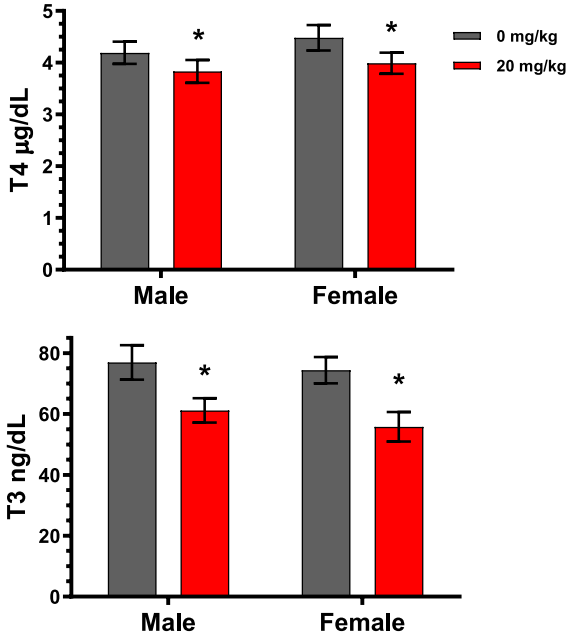

Fig. 2. Mean ± SEM T4 (above) and T3 (below) for the exposed and control groups on postnatal day 22. * = $P < 0.05$ vs. control.

Sigma-Aldrich) in an artificial breast milk as described in Markowski et al. [22]. All animal procedures complied with approved institutional animal care protocols and were in accordance with NIH guidelines [18]. Animal care and welfare were supervised by a veterinarian.

2.2. Tissue collection

On PND22, one male and female pup from each litter were randomly selected, decapitated, and trunk blood and brains were collected. Brains were rapidly removed, immersion-fixed in 4% paraformaldehyde for 48-hrs and transferred to a 20% sucrose solution until processed. Trunk blood was centrifuged and the supernatant was stored at −80 °C until analysis.

2.3. Thyroid hormone radioimmunoassay

Serum from one male and female from 10 control litters and 9 exposed litters was used for total T3 and T4 assays where thyroid hormones compete with ^{125}I-labeled T3 or T4 for binding to the antibody (Coat-A-Count product numbers TKT31 and TKT41, respectively; Siemens, Inc.). Briefly, 50 µl (T3) or 25 µl (T4) of calibrators or thawed serum was added to the antibody-coated tubes along with ^{125}I total T3 or T4. Tubes were incubated for 2 hrs at 37 °C, solutions were decanted, and any excess ^{125}I-labeled hormone was drained. Antibody-bound ^{125}I-labeled hormone was then quantified in a gamma counter for 1 min. Assays for all calibrators were performed in duplicate. A calibration curve was generated by plotting log of% calibrator bound vs. the log of calibrator concentration. This curve was then used to calculate the concentration of total T3 or T4 per sample. Intrassay variability was determined by taking the mean of%CV for calibrators and samples and found to be 8.08% and 4.12% for T3 and T4, respectively.

2.4. Morphometry in the dentate gyrus

Brains were removed from cryoprotectant, snap frozen on dry ice, and 20 µm coronal sections were cut on a cryostat (Leica, CM 1950). Sections were mounted in sequence, heated to 60 °C for 1hr, processed with a series of dehydration and rehydration steps, and stained with a 0.1% solution of cresyl violet. Slides were allowed to dry and coverslipped.

Four matched brain sections containing the dentate gyrus were identified for each of 5 control males, 4 control females, 5 decaBDE males, and 6 decaBDE females. Measurements from the 4 sections per animal were averaged prior to analysis. The appearance of the hippocampus in the sections examined in our PND22 animals resembled that of the adult mouse at −1.58 to −1.94 bregma [26] or positions 274–260 in the PND28 brain presented in the Allen Brain Atlas [1].

Images of the brain sections were taken at a magnification of 10x using a Zeiss AxioImager.A2 microscope system with an AxioCam ICc 3 camera running on a 64-bit Windows 7 computer. Individual images were stitched together to create a complete image of the hippocampus using the FIJI application of ImageJ software. Stitched images were scaled to micrometers and linear height and width measurements of the dentate gyrus and the total hippocampus in a single hemisphere were collected in each section (see Fig. 1). Contour tracing with the ImageJ polygon selection tool was used for area measurements of the granular layer of the dentate gyrus, the hilus, and the hippocampus proper (fields CA1, CA2, CA3, and CA4).

2.5. Glia immunohistochemistry

Different animals were used for the glial fibrillary acidic protein (GFAP) procedures than the cresyl violet staining. Four matched sections containing the dentate gyrus were available for analysis for each of 4 control males, 4 control females, 5 decaBDE males, and 6 decaBDE females. Brains were sectioned at 30 µm and free-floated in cryoprotectant at −20 °C until processing. Tissue was stained for marker using the primary antibody rabbit anti-GFAP (Dako, 1:2000). To visualize, sections were incubated in biotinylated goat anti-rabbit IgG secondary antibody (Vector Laboratories, 1:2000), avidin-biotin complex (Elite), and a 3,3-diaminobenxadine (DAB) substrate kit (Vector Laboratories). Slides were dried and coverslipped.

Astrocyte density was measured in three regions of interest (ROI) in the GFAP-stained sections: the hilus, subgranular zone (SGZ), and granular layer (GL). To accomplish this, the hippocampus was imaged at 20x and individual images were stitched together using FIJI. Stitched images were scaled to micrometers and contour tracing with the ImageJ polygon selection tool was used to demarcate the ROIs and measure their areas. GFAP-positive cell bodies that fell completely within the ROI boundaries were exhaustively counted in each section. Density measurements from the multiple sections per animal were averaged prior to analysis.

Table 1
Mean ± SEM Morphometric Measurements in PND22 Mouse Hippocampus.

	Hippocampus width (mm)	Hippocampus height (mm)	Dentate Gyrus width (mm)	Dentate Gyrus height (mm)	Hippocampus area (mm^2)	Dentate Gyrus area (mm^2)
DecaBDE, male	1.25 ± 0.044	0.504 ± 0.036	0.643 ± 0.027	0.263 ± 0.012	0.095 ± 0.006	0.061 ± 0.005
Control, male	1.32 ± 0.029	0.507 ± 0.023	0.684 ± 0.026	0.282 ± 0.008	0.101 ± 0.003	0.062 ± 0.005
DecaBDE, female	1.31 ± 0.018	0.546 ± 0.023	0.714 ± 0.018	0.265 ± 0.007	0.099 ± 0.003	0.064 ± 0.002
Control, female	1.36 ± 0.049	0.523 ± 0.019	0.732 ± 0.026	0.249 ± 0.010	0.098 ± 0.006	0.060 ± 0.003

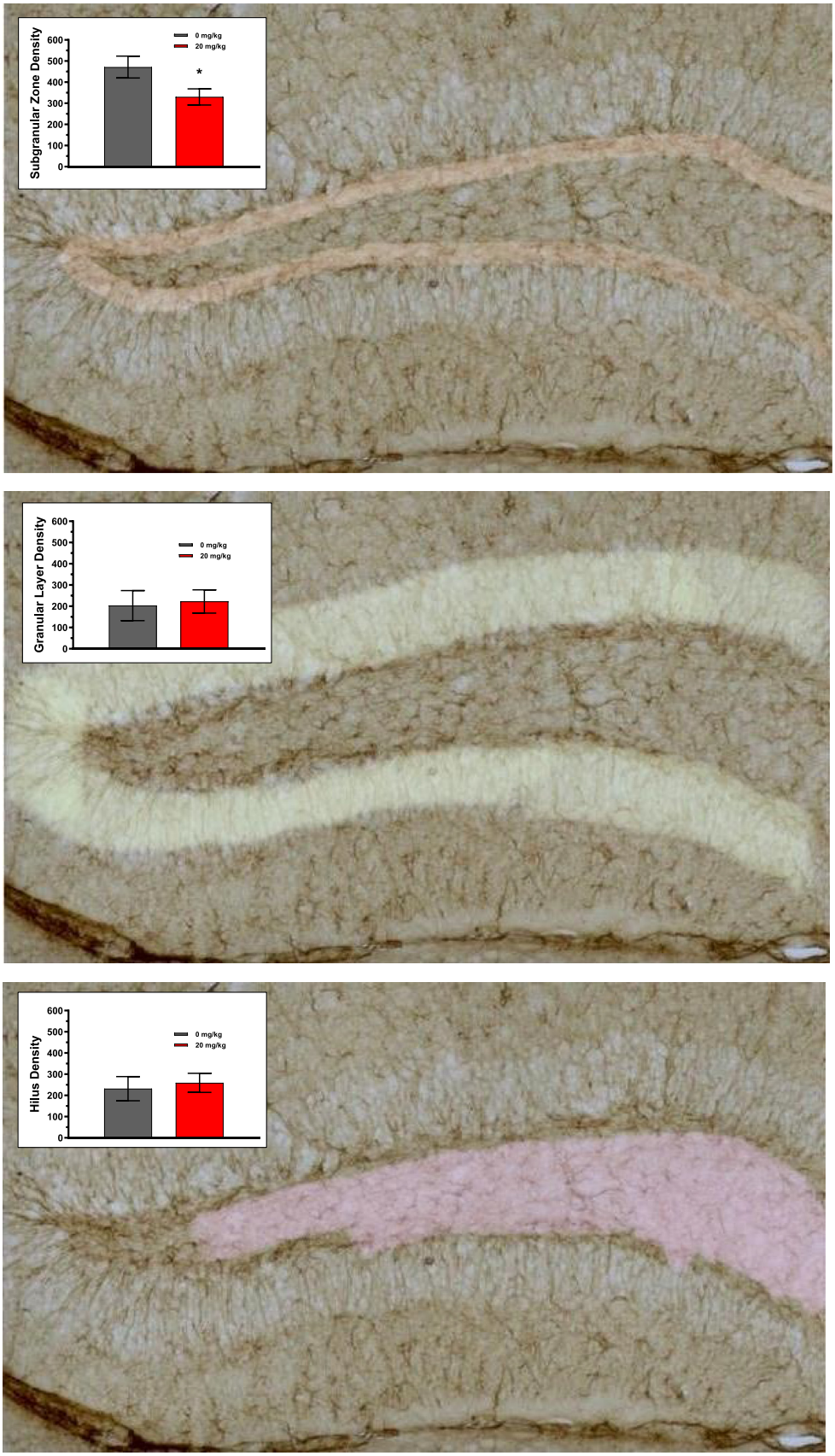

Fig. 3. Representative images of immunohistochemical stain for astrocyte marker GFAP taken at 20x magnification. The subgranular zone ROI is highlighted in the top panel, the granular layer ROI is highlighted in the middle panel and the hilus ROI is highlighted in the bottom panel. The insets show the respective densities in each ROI. * = $P < 0.05$.

2.6. Statistical methods

Data were analyzed with analysis of variance (ANOVA) with PROC GLM SAS version 9.4 (SAS Institute Inc., Cary, NC). DecaBDE dose and sex served as between-subject factors. The Huynh-Feldt adjustment was used when appropriate. Newman-Keuls multiple range tests were used to make pairwise comparisons. A $P \leq 0.05$ was considered statistically significant.

3. Results

3.1. Thyroid hormone

There were significant effects of decaBDE on serum T4 [$F(1,1) = 4.39$, $P = 0.04$] and T3 [$F(1,1) = 4.34$, $P = 0.04$], with lower levels of both hormones in the decaBDE-exposed animals (see Fig. 2). There were no effects of sex on T4 or T3.

3.2. Area and length measurements

There were no effects of decaBDE or sex on any of the length or area measurements in the cresyl-violet stained sections containing total hippocampus and dentate gyrus (Table 1).

3.3. Astrocyte density

There was a significant effect of decaBDE on astrocyte density [$F(1,1) = 5.06$, $P = 0.04$] in the SGZ, with lower density in the decaBDE-exposed animals compared to controls (see Fig. 3). DecaBDE did not affect astrocyte density in the hilus or GL. There were no effects of sex in any of the ROIs.

4. Discussion

The current study found that mice exposed to 20 mg/kg decaBDE from PND1-21 had significantly less total T3, total T4, and lower density of GFAP-positive astrocytes in the hippocampal SGZ on PND22. The effect on astrocytes was limited to the SGZ as it was not observed in the adjacent hilus or GL. The effects in the SGZ did not appear to be the consequence of a global impairment of brain development as we did not observe any differences of linear height or length of the hippocampus in the sections that were examined. Nor were there differences in the total area of the dentate gyrus or the hippocampus proper.

In the current study, both male and female mice were affected, unlike our larger behavioral study where male littermates were more impaired by decaBDE exposure [22]. In that study, exposed males responded with shorter interresponse times (IRTs) and consequently earned fewer reinforcements during a DRL30 schedule of food reinforcement. Hippocampal integrity is essential for DRL performance. Rats that have had the neocortex removed can still acquire efficient DRL behavior with training but animals with hippocampal lesions continue to respond with short IRTs that reduce reinforcement [19,20]. The shortened IRTs following hippocampal manipulations have been interpreted as a consequence of impaired timing and/or a reduction of collateral behaviors that tend to move the animal away from the response lever in the operant chamber.

The present results add to a growing body of decaBDE effects on hippocampal development. Fujimoto et al. [8] observed a reduction of T3 and T4 as well as a reduction of oligodendrocytic density in the rat cingulate cortex following dietary exposure to decaBDE from GD10-PND20. Saegusa et al. [35] reported an increase in the number of immature interneurons in the rat dentate gyrus following the same exposure procedure. This group interpreted the neuronal increase on PND20 as a compensatory response to disrupted migration following impaired neurogenesis. Xu et al. [49] examined the other postnatal proliferative region in the mouse brain, the subventricular zone, following decaBDE exposure. Maternal decaBDE administered from gestation day 6 to postnatal day 16 reduced the percentage of stem cells in subventricular zone that ultimately give rise to the interneurons that populate the olfactory bulb. DecaBDE also reduced the number of newborn neurons, and impaired their migration and dendritic development.

The dentate gyrus is a late-developing structure [45]. Neurogenesis in the mouse dentate gyrus peaks during the first postnatal week but then continues throughout the juvenile and adult stages [16]. Xing et al. [48] previously found that decaBDE exposure during the lactational period, rather than in utero, impaired long-term potentiation in the rat dentate gyrus when assessed in adulthood. Consequently, it is not surprising that the postnatal exposure procedure employed in the current study impacted the proliferative SGZ, an important source of neural stem cells. Since both mature granule cells and mature astrocytes are derived from the same GFAP-positive progenitors [17], it is possible that long-term cellular deficits were produced by decaBDE exposure. A more definitive test of this hypothesis would require additional cell-specific stains as well as additional sampling times during and following the decaBDE exposure to determine whether the current effect was transient, a developmental delay, or a persisting alteration in the hippocampus. Finally, a more comprehensive stereological assessment could reveal volumetric or density differences in hippocampal regions that were not examined in this study.

It is not known if the reduction of astrocyte density in the SGZ and the reduction of serum T4 and T3 were parallel events or if they were causally related. In the healthy neonatal hippocampus, radial glia differentiate into GFAP-positive astrocytes under the influence of T3 [12]. Astrocytes transport T4 across the blood-brain barrier and generate much of the brain's T3 through deiodination processes [24]. Young rats made hypothyroid with propylthiouricil treatments had reduced astrocyte density in the dentate gyrus when examined at PND35 [29]. Perinatal exposure to other endocrine disruptors that reduce serum thyroid hormone also reduce the GFAP-staining intensity and complexity of astrocytic processes in the hippocampus [14,25]. In the current study, decaBDE exposure significantly reduced serum T4 and T3 and disrupted the development of astrocytes in the mouse dentate gyrus. These early effects, noted on PND22, could have contributed to the behavioral deficits in the adult littermates observed in our previous study [22].

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