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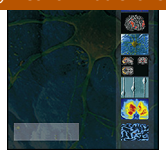

Amelioration of improper differentiation of somatostatin-positive interneurons by triiodothyronine in a growth-retarded hypothyroid mouse strain

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HIGHLIGHTS

- A decrease in parvalbumin-positive neurons in the hippocampus and neocortex of grt mice.
- An increase in somatostatin-positive neurons in the hippocampus of grt mice.
- Hypothyroid neuronal state was recovered by T_3 treatment from postnatal day 0 to 20.

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ABSTRACT

Thyroid hormone (TH) plays an important role in brain development, and TH deficiency during pregnancy or early postnatal periods leads to neurological disorders such as cretinism. Hypothyroidism reduces the number of parvalbumin (PV)-positive interneurons in the neocortex and hippocampus. Here we used a mouse strain (growth-retarded; grt) that shows growth retardation and hypothyroidism to examine whether somatostatin (Sst)-positive interneurons that are generated from the same pool of neural progenitor cells as PV-positive cells are also altered by TH deficiency. The number of PV-positive interneurons was significantly decreased in the neocortex and hippocampus of grt mice as compared with normal control mice. In contrast to the decrease in the number of PV neurons, the number of Sst-positive interneurons in grt mice was increased in the stratum oriens of the hippocampus and the hilus of the dentate gyrus, although their number was unchanged in the neocortex. These changes were reversed by triiodothyronine administration from postnatal day (PD) 0 to 20. TH supplementation that was initiated after PD21 did not, however, affect the number of PV- or Sst-positive cells. These results suggest that during the first three postnatal weeks, TH may be critical for the generation of subpopulations of interneurons.

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1. Introduction

The growth-retarded (grt) mouse was first reported as a spontaneously derived mutant from phenotypically normal siblings of the Snell's dwarf mouse (DW/J strain). The difference in weight between the normal and grt mice become apparent by 3 weeks after birth. However, the weight of the grt mice gradually caught up to that of the normal mice [35]. In grt mice, plasma concentrations of thyroxine (T_4) were significantly lower, whereas levels of thyroid-stimulating hormone (TSH) were greatly elevated [30,35]. Exposure of the thyroid glands of +/+ and +/grt mice to TSH in vitro resulted in the same degree stimulation of free T_4 and free T_3 release from the glands and cAMP production in the glands, but these responses were much weaker in grt/grt thyroid glands [14]. These results indicate that the TSH receptors of these mice are unresponsive to TSH, which likely contributes to the dysfunction of the thyroid gland in grt mice [14,15]. Recently, the grt phenotype was shown to be caused by a single missense mutation in the gene encoding tyrosylprotein sulfotransferase 2 (*Tpst2*) with a change

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from C at nucleotide 798 to G, which leads to the replacement of a highly conserved histidine with glutamine at codon 266 in the sulfotransferase domain [27]. Impaired tyrosine sulfation of TSH receptor molecules by inactivation of TPST2 reduces responsiveness to TSH and causes the functional failure of the thyroid in grt mice [27].

Thyroid hormone (TH) functions in many critical aspects of brain development, including synaptic formation [22], neuronal migration [23], and glial myelination [24], and, consequently, TH deficiency causes mental retardation [25]. Interestingly hypothyroid rats display a decrease in the number of PV-positive interneurons [1], and this phenomenon is reversed by treatment with TH [7].

PV- and somatostatin (Sst)-positive progenitor cells are generated from the medial ganglionic eminence (MGE), tangentially migrate toward the neocortex and hippocampus, and become mature GABAergic interneurons after reaching their destination [3,17]. PV-positive interneurons are detected after postnatal day (PD) 7 in the neocortex and hippocampus [2,26,28] and increase in number during PD14–21 [4]. PV-positive interneurons eventually differentiate into large basket cells and chandelier cells [10,16] and are classified electrophysiologically as fast-spiking cells [11]. Among interneuron subpopulations, Sst-positive interneurons are also generated from the MGE [34] and are detected at PD0 in the hippocampus, earlier than PV-positive neurons [29]. The number of Sst-positive interneurons increases during PD10–15, and they mature to become small basket cells and Martinotti cells, which are regular-spiking and burst-spiking neurons, respectively [12,21]. Circulating T_4 and triiodothyronine (T_3) levels are markedly increased by the second postnatal week in normal mice [5,8], and thus elevation of TH at this stage may strongly influence the normal development of these interneuron subpopulations.

The aim of the present study was to determine whether TH is critical for the development of GABAergic interneurons in mice. We utilized grt mice and investigated the influence of hypothyroidism on the formation of PV- and Sst-positive interneurons, both of which originate from the MGE.

2. Materials and methods

2.1. Animals

Mice were maintained under controlled conditions of temperature (23 ± 1 °C), relative humidity (50 ± 5%), and lighting (lights on 08:00–20:00 h) and were given laboratory chow (Labo MR Breeder; Nosan, Yokohama, Japan) and tap water ad libitum. Male mice with a wild-type phenotype (+/+, +/grt; referred to as "normal") and grt (grt/grt) male mice were obtained by mating wild type (+/+) or heterozygous (+/grt) female mice with heterozygous (+/grt) male mice.

All animal experiments were conducted in accordance with international standards on animal welfare according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and the Animal Experiment Guidelines of the Institutes for Animal Experimentation at Tohoku University and Saitama University.

2.2. Hormone treatment

There were two T_3 treatments. One group of mice was injected with phosphate-buffered saline (PBS, pH 7.4) or T_3 (Sigma–Aldrich Co., St. Louis, MO, USA) from PD0 to 20, and the other group was injected with PBS or T_3 from PD21 to 27. Normal mice ($n = 4$) were injected intraperitoneally with 10 mM PBS (i.e., they did not receive T_3 treatment), and grt mice with PBS ($n = 4$–5) or T_3 in PBS (2 μg/10 g body weight; $n = 4$) once every other day. Brains were collected on the day after the last injection (i.e., a sampling day is at PD21 or 28). The effective dose of T_3 in mice was determined according to a previous study [31].

2.3. Tissue preparation and immunohistochemistry

Mice were deeply anesthetized with sodium pentobarbital (50 mg/kg) and perfused with 0.9% saline followed by 4% paraformaldehyde (PFA) in 0.1 M phosphate buffer (PB, pH 7.4). The brain was post-fixed overnight in 4% PFA, and stored in 30% sucrose in 0.01 M PB (pH 7.4) at 4 °C for 48 h. Thirty-micrometer-thick sections were cut on a cryostat, and free-floating sections were rinsed in 10 mM PBS (pH 7.4). After being washed with PBS containing 0.3% (w/v) Triton X-100 (PBS-T), sections were incubated for 30 min with 5% normal horse or goat serum diluted in PBS-T. The sections were then incubated overnight at 4 °C with mouse anti-PV (1:500; Sigma–Aldrich Co.) or rabbit anti-Sst (1:500; Enzo Life Sciences International, Inc. Plymouth Meeting, PA, USA). After being washed with PBS-T, the sections were treated with 0.1% H_2O_2 to inactivate endogenous peroxidases. After another wash in PBS-T, the sections were incubated with biotinylated anti-mouse or anti-rabbit IgG (1:1000; Vector Laboratories, Burlingame, CA, USA) for 2 h at room temperature, rinsed with PBS-T, and incubated with avidin–biotin complex (ABC; Vector Laboratories) for 1 h at room temperature. The staining was then visualized by incubating the sections in 0.05% diaminobenzidine and 0.02% H_2O_2 in PBS.

2.4. Quantification

Thirty-micrometer serial sections from ∼−1.06 to −3.40 mm caudal to the bregma according to the stereotaxic atlas of Franklin and Paxinos [13] were cut on a cryostat and preserved in 200 μl cryoprotectant (PBS with 15% sucrose, 30% ethylene glycol solution) per well. Sections from each animal were analyzed at 210-μm intervals. After immunostaining, microscopic images of these sections were taken with a CCD camera and processed using Adobe Photoshop CS6 (Adobe Systems, San Jose, CA, USA). The area of the hippocampus (the pyramidal cell layer including CA1 to CA4 and the granular cell layer of the dentate gyrus) and the area of the whole neocortex (the motor, somatosensory, visual and association cortex) in each section were measured using ImageJ (National Institutes of Health, Bethesda, MD, USA). The density of immunoreactive cells in each section was calculated by dividing the number of Sst- or PV-positive cells by the area of the hippocampus or the neocortex. All data were expressed as the mean ± SEM. Comparisons with control (PBS-treated normal mice) and study groups (PBS-treated grt mice and T_3-treated grt mice) were analyzed with one-way ANOVA followed by Tukey's multiple comparison test. P values of <0.05 were considered statistically significant. Statistical analysis was performed with GraphPad Prism 5 (GraphPad Software Inc., San Diego, CA, USA).

3. Results

3.1. Changes in the number of PV-positive cells in the neocortex and hippocampus of grt mice

PV-positive cells were widely distributed in the neocortex (see supplementary Fig. 1). Although the cortical area, including the area ∼−1.06 to −3.40 mm caudal to the bregma, contains the motor cortex, somatosensory cortex, visual cortex, and association cortex, the results of an immunohistochemical study showed no significant differences among the cortical regions. Thus a numerical value of the neocortex shows changes of the number of cells in the whole

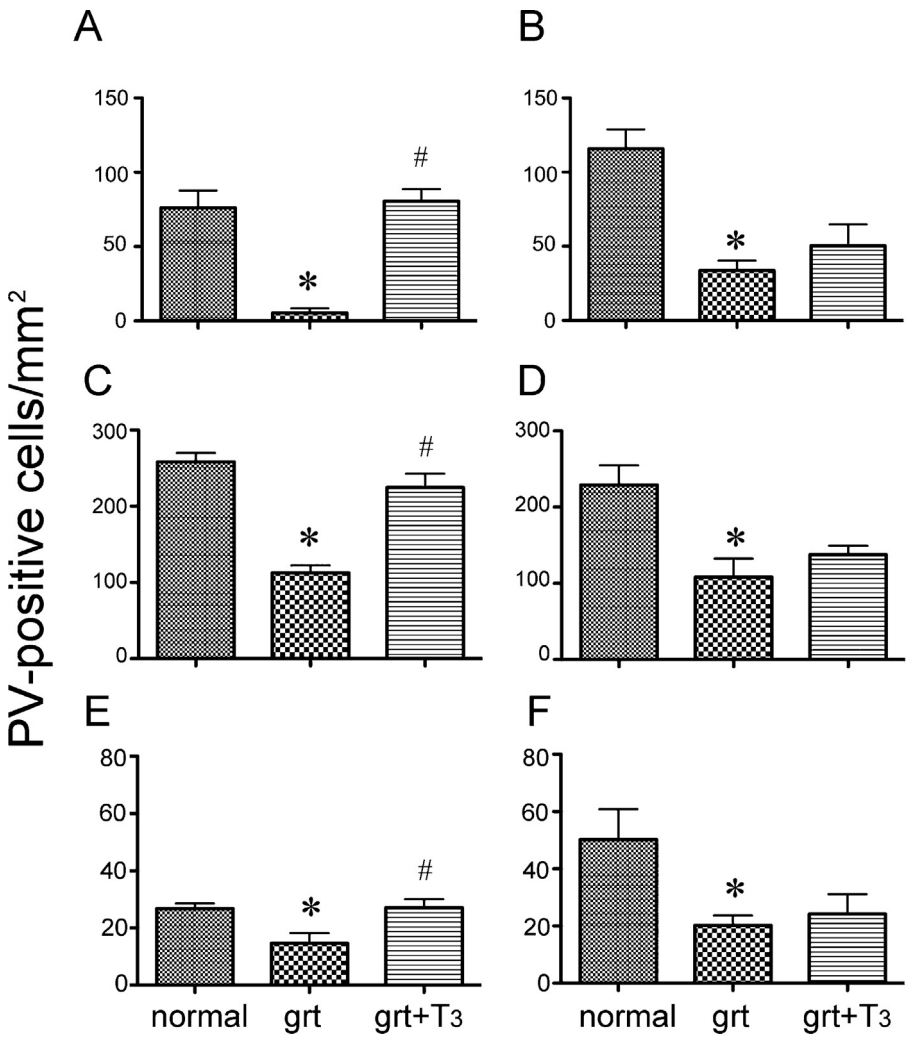

Fig. 1. PV-positive interneuron density in the neocortex and hippocampus of grt mice. Graphs show the PV neuron density in the neocortex (A, B) and cornus ammonis (C, D) and dentate gyrus (E, F). Quantification of the number of PV-positive interneurons in the region was done at PD 21 (A, C, E) and at PD28 (B, D, F). Data were expressed as the mean ± SEM. $^{*}P < 0.05$ (normal vs. grt), $^{\#}P < 0.05$ (grt vs. grt + T_3).

cortex. At PD21, the number of PV-positive cells in the neocortex of grt mice (5.4 ± 2.9 cells/mm^2) was 93% lower than that of normal mice (76.0 ± 11.8 cells/mm^2; Fig. 1A). Injection of grt mice with T_3 beginning at PD0 (2 μg/10 g body weight) significantly increased the number of PV-positive cells (80.0 ± 8.09 cells/mm^2) to a number that was equivalent to the basal level in normal mice (Fig. 1A). At PD28, the number of PV-positive cells in grt mice (33.6 ± 6.6 cells/mm^2) was 70% lower than that of normal mice (115.8 ± 13.1 cells/mm^2), although the number of PV-positive cells was higher than that at PD21 (Fig. 1A, B). T_3 treatment beginning at PD21 had no effect on the number of PV-positive cells in grt mice (50.4 ± 14.2 cells/mm^2; Fig. 1B).

In the hippocampus, PV-positive cells were localized mainly in the pyramidal cell layer of the CA regions and the granular cell layer of the dentate gyrus (see supplementary Fig. 2). The changes in the number of PV-positive cells among the experimental groups were similar to those in the neocortex, and the number of PV-positive cells in the CA regions of grt mice (112.8 ± 9.6 cells/mm^2) was 56% lower than that of normal mice (258.4 ± 11.4 cells/mm^2) at PD21 (Fig. 1C). Treatment of grt mice with T_3 beginning at PD0 significantly increased the number of PV-positive cells in the CA regions (224.6 ± 18.0 cells/mm^2) to a number that was equivalent to the basal level in normal mice (Fig. 1C). At PD28, the number of PV-positive cells in the CA regions of grt mice (108.4 ± 24.2 cells/mm^2) was decreased by 53% as compared with that of normal mice (229.1 ± 25.7 cells/mm^2; Fig. 1D). T_3 treatment beginning at PD21 had no effect on the number of PV-positive cells in the CA regions of grt mice (137.9 ± 11.2 cells/mm^2; Fig. 1D). In the granular cell layer of the dentate gyrus, the number of PV-positive cells in grt mice at PD21 (14.5 ± 3.5 cells/mm^2) was 54% lower than that of normal mice (26.7 ± 1.8 cells/mm^2; Fig. 1E). Treatment of grt mice with T_3 beginning at PD0 significantly increased the number of PV-positive cells (27.1 ± 2.9 cells/mm^2) (Fig. 1E). At PD28, the number of PV-positive cells in grt mice (20.2 ± 3.4 cells/mm^2) was reduced by 60% as compared with that of normal mice (50.2 ± 10.5 cells/mm^2; Fig. 1F), and the number of PV-positive cells in the dentate gyrus was slightly higher than that at PD21. T_3 treatment beginning at PD21 had no effect on the number of PV-positive cells in grt mice (24.2 ± 6.9 cells/mm^2; Fig. 1F).

3.2. Changes in the number of Sst-positive cells in the neocortex and hippocampus of grt mice

Sst-positive cells were widely distributed in the neocortex (see supplementary Fig. 3) of the grt mice, and this distribution was indistinguishable from that of normal mice. At PD21, no significant difference was found in the number of Sst-positive cells in the neocortex among the experimental groups (normal

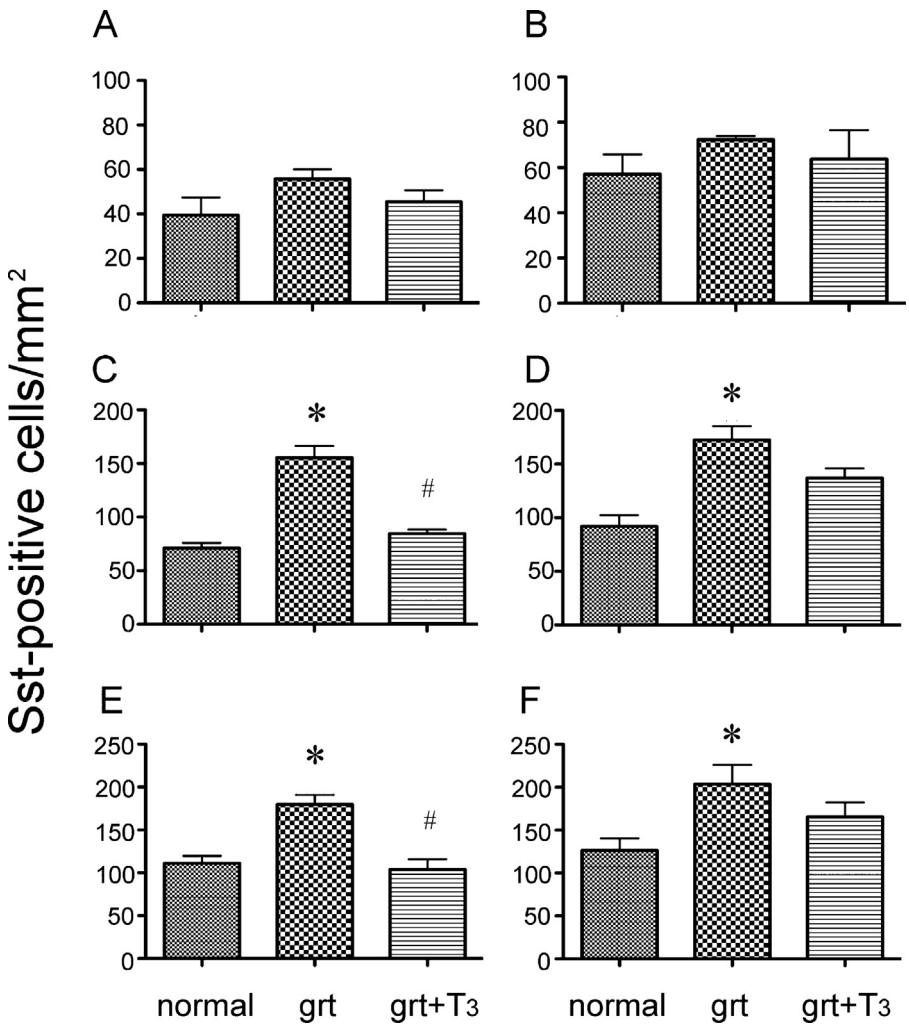

Fig. 2. Sst-positive interneuron density in the neocortex and hippocampus of grt mice. Graphs show the Sst neuron density in the neocortex (A, B) and stratum oriens (C, D) and hilus (E, F). Quantification of the number of Sst-positive interneurons in the region was done at PD 21 (A, C, E) and at PD28 (B, D, F). Data were expressed as the mean ± SEM. $^{*}P < 0.05$ (normal vs. grt), $^{\#}P < 0.05$ (grt vs. grt + T_3).

mice: 39.4 ± 8.0 cells/mm^2, grt mice: 55.7 ± 4.2 cells/mm^2, grt + T_3: 45.5 ± 5.0 cells/mm^2; Fig. 2A). At PD28, we found no significant difference in the cell number in the neocortex among the experimental groups (normal mice: 57.0 ± 8.7 cells/mm^2, grt mice: 72.3 ± 1.6 cells/mm^2, grt + T_3: 63.6 ± 12.8 cells/mm^2), and the number of Sst-positive cells in the neocortex was slightly higher than that at PD21 (Fig. 2A, B).

In the hippocampus, Sst-positive cells were localized mainly in the stratum oriens and the hilus of the dentate gyrus; some cells were scattered in the stratum radiatum and the CA regions (see supplementary Fig. 4). At PD21, the number of Sst-positive cells in the hilus of the grt mice (155.4 ± 10.8 cells/mm^2) was 118% greater than that of normal mice (71.1 ± 4.8 cells/mm^2; Fig. 2C). Treatment of grt mice with T_3 beginning at PD0 significantly decreased the number of Sst-positive cells (84.5 ± 3.9 cells/mm^2; Fig. 2C). At PD28, the number of Sst-positive cells in grt mice (172.5 ± 12.8 cells/mm^2) was 88% higher than that of normal mice (91.9 ± 10.2 cells/mm^2; Fig. 2D). However, T_3 treatment beginning at PD21 had no effect on the number of Sst-positive cells in the hilus of grt mice (137.0 ± 8.9 cells/mm^2; Fig. 2D). The number of Sst-positive cells in the stratum oriens of grt mice (179.6 ± 11.3 cells/mm^2) was 62% higher than that of normal mice (111.0 ± 8.6 cells/mm^2) at PD28 (Fig. 2E). Treatment of grt mice with T_3 beginning at PD0 significantly decreased the number of Sst-positive cells (103.9 ± 11.6 cells/mm^2) to a number equivalent to the basal level of normal mice (Fig. 2E). At PD28, the number of Sst-positive cells in the stratum oriens of grt mice (192.6 ± 19.5 cells/mm^2) was 52% higher than that of normal mice (126.1 ± 13.9 cells/mm^2; Fig. 2F). However, T_3 treatment beginning at PD21 had no effect on the number of Sst-positive cells in grt mice (165.5 ± 16.8 cells/mm^2; Fig. 2F).

4. Discussion

We demonstrated that TH deficiency led to impairment in the development of parvalbumin- and somatostatin-positive interneurons in the brains of grt mice and that the defect was ameliorated by exogenous T_3 administration during an early postnatal period (PD0–20).

Goitrogen-induced hypothyroidism induces a decrease in the number of PV-positive interneurons in the neocortex and hippocampus of the rat [1,7]. The number of PV-positive interneurons in the rat brain is also decreased in a dose-dependent manner by treatment with propylthiouracil (PTU) and the lost PV-positive cells in the hypothyroid brain are restored by treatment with T_4 from PD8 to 14 [7]. Consistent with these studies, our results showed that the number of PV-positive neurons was reduced in the brains of grt mice, and their numbers were restored with T_3 treatment

from PD0–20. Therefore, TH is likely to play an important role in the development of PV-positive interneurons, at least in rodents. On the other hand, TH receptor α1 mutant mouse exhibits low affinity to TH causes a decrease in the number of PV-positive interneurons [32,33]. Therefore TH action through receptor subtype α1 may play a critical role in the normal development of GABAergic interneurons.

In addition, we found for the first time that the number of Sst-positive neurons in the hippocampus was increased in grt mice. Kato et al. reported that the amount of Sst in the hippocampus and other brain regions, including the neocortex, of adult rats is increased following treatment with PTU from PD0–19 [9]. The reason for the discrepancy between our observation of no change in Sst-positive cells in the neocortex and Kato et al.'s report of an increase in this region is not clear, but it may partly be a result of species differences and/or methodological and assay system differences. However, the changes in the number of Sst-positive cells in the hippocampus may be considered TH dependent, because the cell number in grt mice was restored to the number in normal mice by treatment with T_3. In the present study, the effect of exogenous T_3 on the number of PV- and Sst-positive cells in grt mice was observed only during the first three postnatal weeks, consistent with the idea that these interneurons are responsive to TH only during the early postnatal stage. Furthermore, although improper differentiation of interneurons is improved by a short-term TH treatment of 1 week as described elsewhere [7], T_3 treatment from PD 21 to 27 had no effect on the number of interneuron subpopulation. Therefore, critical period of the generation of subpopulations of interneurons is assumed to exist during the first three postnatal weeks.

One possible mechanism by which TH could affect the development of interneurons involves bone morphogenetic protein-4 (BMP4). Increased expression of BMP4 mRNA occurs in the neocortex during PD7–14, and this term coincides with the appearance of PV-positive interneurons in the neocortex [20]. In addition, overexpression of BMP4 induces an increased in the number of PV-positive interneurons and a reduction in the number of Sst-positive interneurons in the dentate gyrus of the hippocampus [20]. These results raise the possibility that BMP4 directly regulates the differentiation of PV- and Sst-positive interneurons. Interestingly, the expression level of BMP4 is markedly decreased in the hypothyroid neonatal brain as compared with the euthyroid state, and the decrease in BMP4 is restored by TH supplementation [18]. Thus, we speculate that a reduction in BMP4 signaling caused by TH deficiency impairs the differentiation of interneurons. However, such a simplistic mechanism for the effects of TH activity on the differentiation of interneuron subpopulations is not likely, because the rate of change in the PV-positive cell number in grt mice did not match that of Sst-positive interneurons. Moreover, although PV-positive neurons were markedly decreased in the neocortex of grt mice, no significant change was found in Sst-positive interneurons. Hence, these results suggest that the action of TH may be unrelated to regulation of the interneuron cell lineage such as the switch from PV progenitor cells to Sst progenitor cells. Regarding an increase in Sst-positive neurons, one possibility is a compensatory action that occurs in response to a reduction in PV-positive neurons. Because Sst-positive neurons in the hippocampus are increased by bicuculline treatment [19], an increase in Sst-positive neurons may be due to an imbalance in the excitatory and inhibitory systems that results from a reduction in PV-positive interneurons.

Normal mice showed a marked transient rise in serum T_4 level at 2 weeks after birth. In grt mice, however, serum concentrations of T_4 were very low from neonatal period through adulthood, and transient rise in T_4 level was not observed [35]. This transient rise in serum T_4 level at about 2 weeks of age in normal mice was also reported by other investigators [6,8]. These reports and our results support that adequate thyroid hormone levels in the neonatal period are important for the development of interneuron subpopulations in the brain.

Elucidating the mechanism of interneuron differentiation may increase our understanding of the pathogenic mechanisms of certain types of intellectual disabilities, such as cretinism.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neulet.2013.11.052.

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