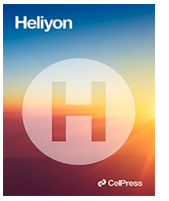
Heliyon 9 (2023) e13161

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Iodide intake during pregnancy and lactation stimulates KLF9, BDNF expression in offspring brain with elevated DHA, EPA metabolites

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ARTICLE INFO

Keywords:
Iodide
KLF9
BDNF
DHA
EPA
Brain

ABSTRACT

To investigate the effect of different iodide intake during pregnancy and lactation on thyroid function, docosahexaenoic acid (DHA), Eicosapentaenoic acid (EPA) metabolites, the expression of Krüppel-like factor KLF9 (KLF9), brain-derived neurotrophic factor (BDNF) in brain in offspring rats. In both male and female offspring rats, serum FT3, FT4 levels and the expression of KLF9, thyroid hormone receptors (TR)α, TRβ and BDNF in the hippocampal region and cerebellum were significantly increased in 5 times higher-than-normal pregnant iodide intake (5 HI) and 10 times higher-than-normal pregnant iodide intake (10 HI) group. The median levels of DHA metabolite (17-HDoHE) and EPA metabolites (15-HEPE, 17,18-EEQ, 9-HEPE and 14,15-DiHETE) were significantly increased in 5 HI and 10 HI group of offspring rats. Serum DHA, EPA metabolites and KLF9 as well as BDNF expression in brain might be potential iodine status biomarkers to reflect brain development in offspring.

1. Introduction

Iodine is an essential element for thyroid hormone (TH) synthesis [1], which is essential for normal brain development. Pregnant women and their fetuses are sensitive to iodide deficiency or excess, as it carries a risk of iodine-induced thyroid dysfunction, which may lead to the development of hypothyroidism, hyperthyroidism, goitre or autoimmune thyroid disease [2].

TH, mainly 3,5,3′-triiodothyronine (T3), act through thyroid hormone receptors (TRs) regulated Krüppel-like factor 9 (KLF9) expression [3]. KLF9 is a direct TRs target gene, the increase in KLF9 mRNA parallels the postnatal rise in circulating thyroid hormone (T3) [4]. Epigenome-wide association study of thyroid function traits on 863 pregnant women of 16–20 weeks gestation in Perth, identifies the associations of free T3 with KLF9 [5]. KLF9 plays a key role in thyroid hormone-dependent actions on neurogenesis [6,7]. In addition, significant associations between the KLF9 locus at 9q21 and the BDNF locus at 11p14 were identified in 26,620 Japanese subjects [8]. BDNF is one of the most distributed neurotrophins in the mammalian brain, and plays an important role in development and plasticity of synapses [9].

We previously reported that the increased levels of epoxyeicosatrienoic acids (EETs) and hydroxyeicosatetraenoic acids (HETEs)

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https://doi.org/10.1016/j.heliyon.2023.e13161
Received 26 October 2022; Received in revised form 16 January 2023; Accepted 19 January 2023
Available online 21 January 2023

might help to ameliorate cardiac dysfunction, hypertension and dyslipidemia in high iodide intake-induced thyroid dysfunction after iodide intake adjustment [10]. Evidence for cross-talking mechanisms were found among the n-3 polyunsaturated fatty acids (PUFA), TH signaling and BDNF as well. Souza et al. showed that n-3 PUFA effects on lipid metabolism are dependent on TH signaling in liver of hypothyroid rats, the ability of n-3 PUFA to induce enhancement in liver expression of TRβ was lost in hypothyroidism [11]. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) synthesized from PUFA can exert neuroprotective functions by up-regulating the expression of BDNF [12,13,14]. However, the effect of different iodide intake during pregnancy and lactation on thyroid function, on thyroid response element KLF9 in offspring brain, and on serum DHA, EPA metabolites remains largely unknown.

Considering the similarities in both PUFA and KLF9, which have been specifically interacted with T3, TRs and BDNF, prompted us to see whether they could have overlapping neuroprotective mechanisms contributing to both n-3 PUFA and KLF9 actions. Determining the changes in PUFA and KLF9 related to TH, TRs and BDNF expression may help in early detection, and aid in better understanding their roles in different iodide intake-induced thyroid dysfunction during pregnancy and lactation in maternal and offspring rats, and its impact on brain development with potential physiological and therapeutic implications.

2. Materials and methods

This study was approved by the Institutional Animal Care and Use Committee of Tianjin Medical University (no. TMUaMEC 2016054).

2.1. Animals and administration

Healthy Wistar rats were obtained from Beijing Vital River Laboratory Animal Technology Co., Ltd. The animals were housed in the specific pathogen-free (SPF) level in the Experimental Animal Center of Tianjin Medical University. Seven-week-old female Wistar rats were mated with fertile males (2:1). The presence of a vaginal plug or sperm in the vaginal smear was indicative of pregnancy (Day 0 of gestation, GD 0). Pregnant rats were randomly divided into four groups (n = 6 for each group): normal adult iodide intake (NAI, 7.5 μg/d), normal pregnant iodide intake (NPI, 12.5 μg/d), 5 times higher-than-normal pregnant iodide intake (5 HI, 62.5 μg/d) and 10 times higher-than-normal pregnant iodide intake (10 HI, 125 μg/d). Maternal rats were continuously administered above diet until postnatal day 16 (PN16), and the male and female offspring rats were sacrificed on PN16.

2.2. Measurement of FT3, FT4 and TSH in serum by enzyme-linked immunosorbent assay (ELISA)

Blood samples were collected from the inner canthus of maternal rats or the femoral artery of offspring rats on PN16. Serum was separated and stored at −80 °C for subsequent measurement of FT3, FT4 and thyrotropin (TSH) by using the rat specific ELISA kits (Catalogue number: ml202846, ml002849 and ml002877, Meilian Biological Technology, Shanghai, China).

2.3. Quantitative real-time PCR analysis

Total RNA from offspring rat brain sections that contained either the hippocampus or cerebellum was prepared using TRIzol reagent (Life Technologies, California, USA). The reverse transcriptase reaction was conducted to synthesize complimentary cDNAs. Amplifications were performed with an initial denaturation step at 95 °C for 5 min, followed by 40 cycles of 95 °C for 15 s, 60 °C for 1 min, and 95 °C for 15 s, 37 °C for 5 min by using a Real-time PCR Detection System (LC480II, Switzerland). The value of relative mRNA expression was normalized to glyceraldehyde 3-phosphate dehydrogenase (GAPDH). The $2^{-\triangle\triangle Ct}$ method was used. Primers were constructed for KLF9: 5'-TGG AACATCAAGCTCCCTTT-3' (forward), 5'-GCAGGGGCTAAT TT CAAGGT-3' (reverse); for TRα: 5'-GACAAGGCCACCG GTTATCACTAC-3' (forward), 5' -GA TCTTGTCGATGACGCAGCA-3' (reverse); for TRβ: 5'-GGGTACCACTATCGCT GCATCAC-3' (forward), 5'-TCCCACTGCC TTGAGGACAAC-3' (reverse); for GAPDH: 5'-GACATGCCGCCTGGAGAAAC-3' (forward), 5'-AGCCCAGGATGC CCTTTAGT-3' (reverse).

2.4. Liquid chromatography-mass spectrometry (LC-MS) analysis

Serum was extracted by solid-phase extraction as described [15]. Chromatographic separation was executed on BEH C18 column (1.7 μm, 100 × 2.1 mm i.d) consisting of ethylenebridged hybrid particles (Waters, Milford, MA, USA) at a flow rate of 0.6 mL/min (column temperature, 25 °C). The polyunsaturated fatty acid (PUFA) metabolites were profiled by multiple reaction monitoring scans in negative mode, which involved use of a 5500 QTRAP hybrid triple quadrupole linear ion-trap mass spectrometer (AB Sciex, Foster City, CA, USA) equipped with a turbo ion-spray electrospray ionization source.

2.5. Immunohistochemistry and immunofluorescence staining

Formalin-fixed and paraffin embedded brain sections (4 μm) were deparaffinized in xylene twice for 5 min each, rehydrated in absolute ethanol for 10 min followed by 90%, 80% and 70% ethanol for 5 min each. For immunohistochemistry, sections were autoclaved in sodium citrate buffer at pH 6.0 for 10 min, then incubated with rabbit polyclonal anti-KLF9 antibody (1:500, Abcam, UK) for 1 h at 37 °C, and secondary antibody (1:300, Abcam, UK) for 20 min at 37 °C. The chromogen substrate was diaminobenzidine [16]. For immunofluorescence, sections were incubated with rabbit polyclonal anti-KLF9 antibody (1:500, Abcam, UK) and mouse

monoclonal anti-thyroid hormone receptor β (TRβ) antibody (1:500, Abcam, UK) at 4 °C overnight. Then the sections were incubated in the dark for 60 min at 37 °C with secondary antibodies, goat anti-rabbit IgG-FITC and goat anti-mouse IgG-FITC (1:400, Santa Cruz, USA), nuclei were stained with Hoechst 33258, sections were photographed utilizing Zeiss LSM 510 laser confocal microscope (Zeiss, Germany).

2.6. Statistical analysis

SPSS 22.0 was used to perform one-way ANOVA. Differences were considered statistically significant at $p < 0.05$. Pearson correlations were used to detect the relationship between fatty acids and KLF9 mRNA expression, between fatty acids and BDNF mRNA expression. Data were expressed as Mean ± standard deviation (SD), n = 6 for each group. Fatty acids were quantified with use of MultiQuant 2.1 (AB Sciex, Foster City, CA). Fold change (FC) > 2 and $p < 0.05$ represent significant result. Metaboanalyst 3.0 (http://www.metaboanalyst.ca) was used for metabolomic data analysis, interpretation, n = 3 for each group.

3. Results

3.1. High iodide intake during pregnancy and lactation until PN16 elevates FT3, FT4 levels in maternal and offspring rats

In both maternal and offspring rats, compared to NPI group, no significant difference was detected in FT3, FT4 and TSH levels in NAI group ($p > 0.05$), while FT3, FT4 levels were significantly increased ($p < 0.05$), and TSH level was significantly decreased ($p < 0.05$) in both 5 HI and 10 HI group (Fig. 1C–E, H-J, M − O).

Comparison of the brain–body weight ratios among the groups failed to demonstrate a significant difference ($p > 0.05$) (Fig. 1A, B, F, G, K, L).

3.2. High iodide intake during pregnancy and lactation stimulates KLF9, TRα, TRβ and BDNF expression in hippocampal region and cerebellum of offspring rats

In both 5 HI and 10 HI groups, qRT-PCR indicated that the expression of KLF9, TRα, TRβ and BDNF were significantly increased in the hippocampal region and cerebellum in both male and female offspring rats when compared with NPI group ($p < 0.05$) (Fig. 2A and B). While in NAI group, no significant differences were detected when compared with NPI group in both male and female offspring rats ($p > 0.05$) (Fig. 2A and B).

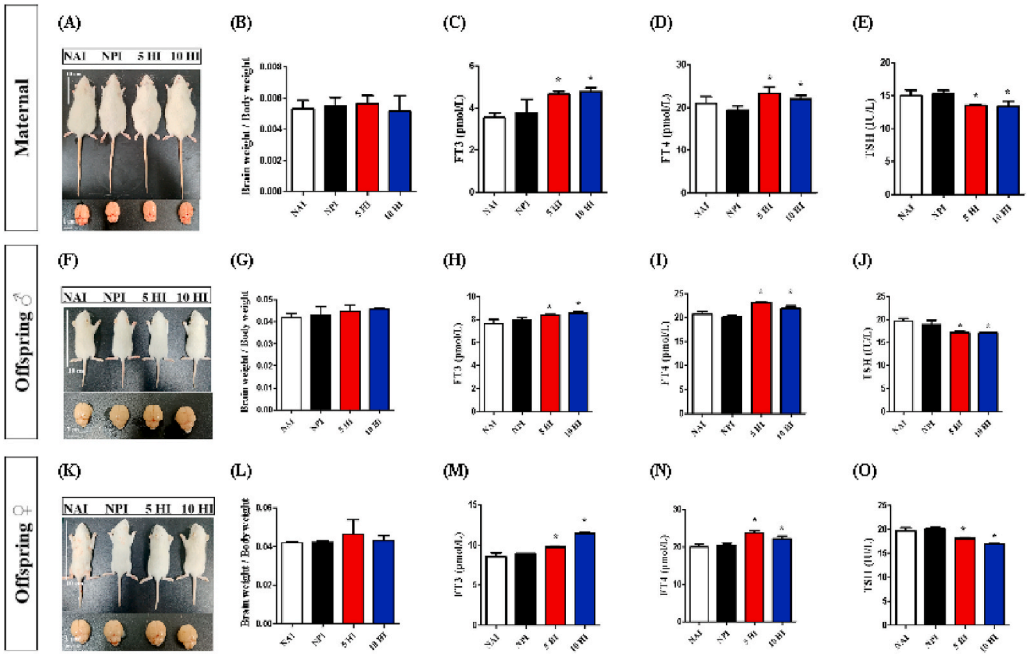

Fig. 1. Comparison of thyroid hormone levels and brain-body weight ratios. (A, F, K) Gross appearance of brains from maternal, male and female offspring rats. (B, G, L) Comparison of brain-body weight ratios. (C−E, H−J, M−O) Serum FT3, FT4 and TSH levels in maternal, male and female offspring rats. FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyrotropin. Each value represents the mean ± SD (n = 6). One-way ANOVA with post hoc LSD multiple comparison test was used. *$p < 0.05$ *vs* NPI group. Scale bars: A, F, K = 10 cm and 1 cm.

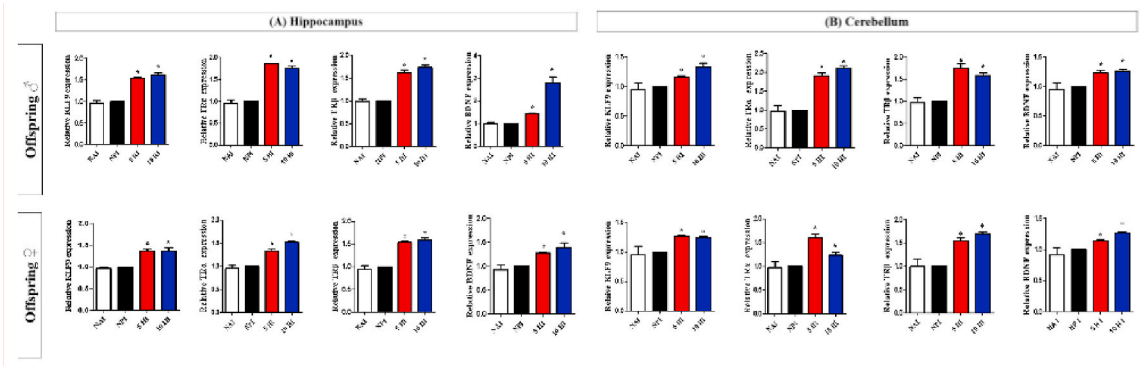

Fig. 2. Expression of KLF9, TRα, TRβ and BDNF in hippocampus (A) and cerebellum (B) by qRT-PCR normalized to GAPDH in both male and female offspring rats. Data are expressed in mean ± SD (n = 6 for each group). One-way ANOVA with post hoc LSD multiple comparison test was used. *$p < 0.05$ *vs* NPI group.

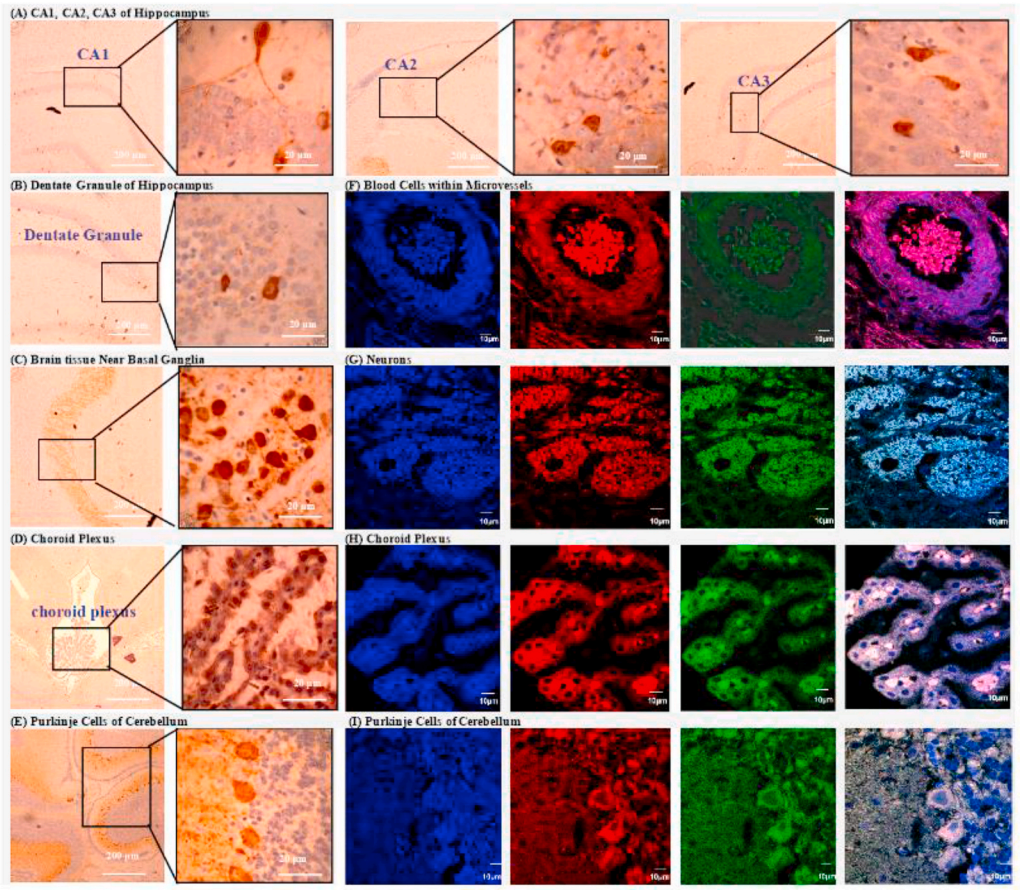

Fig. 3. Representative pathological images of KLF9 expression and its interaction with TRβ in the brain. Positive immunohistochemical staining for KLF9 (brown) in brain were observed in neurons in (A) CA1, CA2, CA3, (B) dentate granule of hippocampus, in (C) brain tissues near basal ganglia, (D) choroid plexus and (E) Purkinje cells of cerebellum. Higher magnifications of the region boxed were shown. Immunofluorescence staining was detected by KLF9 (red), TRβ (green), Hoechst 33258 (blue) and Merge (purple). Positive immunofluorescence staining of KLF9 (red) co-localized with TRβ (green) were detected in (F) blood cells within microvessels, (G) neurons, (H) choroid plexus, and (I) Purkinje cells of cerebellum. Scale bars: A-E = 200 μm and 20 μm, F–I = 10 μm. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3.3. Characteristic distribution of KLF9 and its co-localization with TRβ in brain

DAB immunohistochemistry demonstrated that KLF9-positive cells were detected in CA1, CA2, CA3 and dentate granule of hippocampus, in brain regions near basal ganglia, in choroid plexus and in Purkinje cells of cerebellum (Fig. 3A–E). Using immunofluorescence staining, it was possible to obtain information about the expression of KLF9 and its co-localization with TRβ in blood cells within microvessels, in neurons, in choroid plexus, and in Purkinje cells of cerebellum (Fig. 3F–I).

3.4. High iodide intake during pregnancy and lactation enhances DHA and EPA metabolites in offspring rats, especially in 5 HI group

In male offspring rats, compared to NPI group, the median levels of DHA metabolite (17-HDoHE) and EPA metabolites (15-HEPE, 17,18-EEQ and 9-HEPE) were significantly increased ($p < 0.05$) in 5 HI group. In female offspring rats, the median levels of EPA metabolite (14,15-DiHETE) were significantly increased in both 5 HI and 10 HI group ($p < 0.05$) (Fig. 4D–I). No significant changes were found in other groups when compared to NPI group in offspring rats ($p > 0.05$).

Correlation analysis demonstrated that serum EPA metabolite (9-HEPE) was significantly correlated with KLF9 expression in hippocampus ($r = 0.049$, $p = 0.034$), serum DHA metabolite (17-HDoHE) and EPA metabolites (15-HEPE and 17,18-EEQ) were significantly correlated with BDNF expression in hippocampus ($r = 0.000$, $p = 0.023$; $r = 0.003$, $p = 0.021$; $r = 0.054$, $p = 0.023$) in male offspring rats of 5 HI group (Fig. 4A). In female offspring rats of 5 HI group, EPA metabolite (14,15-DiHETE) was correlated with

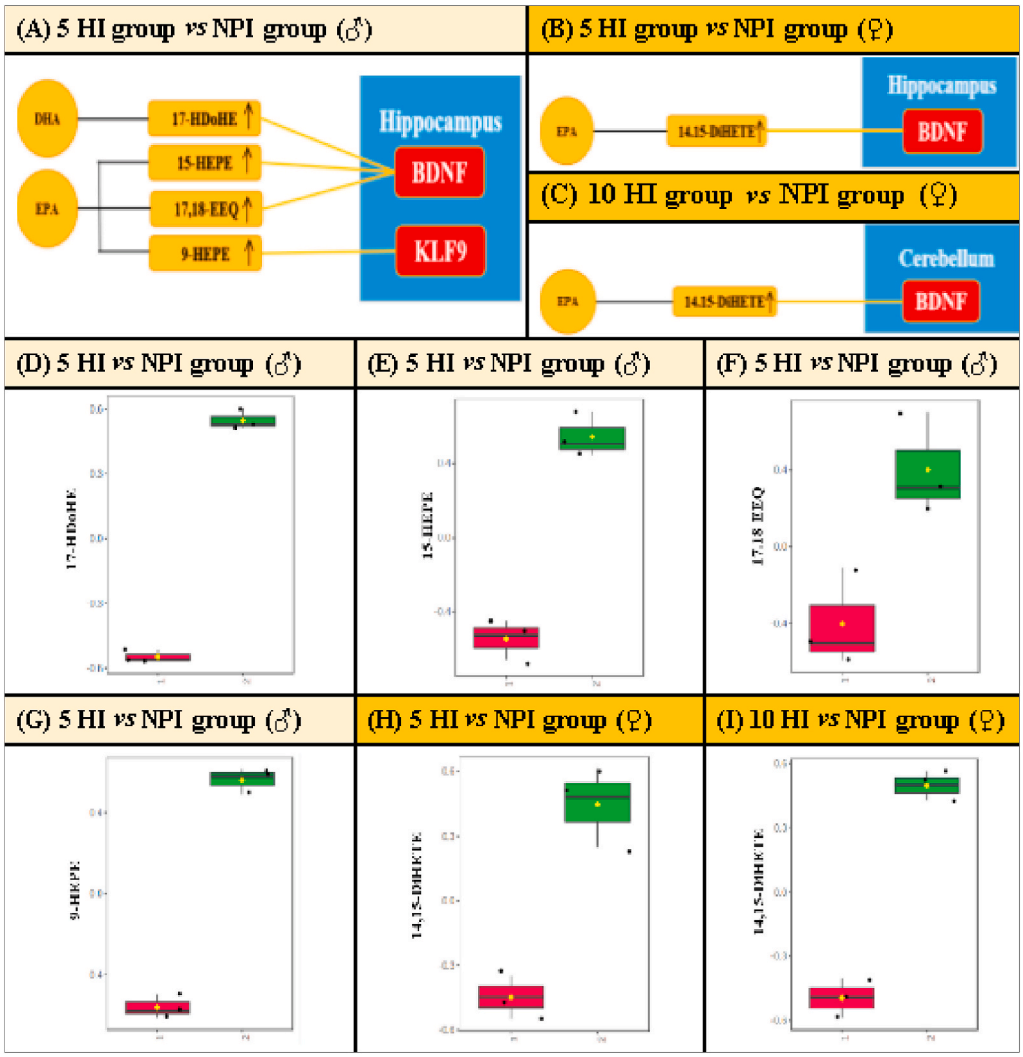

Fig. 4. Effect of iodide intake during pregnancy and lactation on DHA, EPA metabolites in male and female offspring rats and correlation analysis. (A–C) Correlation analysis between significantly changed DHA and EPA metabolites and the expression of KLF9, BDNF in male and female offspring rats. (D–I) Box plots show the significantly changed DHA and EPA metabolites from 5 HI and NPI group, 10 HI and NPI group in male or female offspring rats. The bar in the quartile-indicating box is the median value (n = 3 for each group).

BDNF expression in hippocampus ($r = 0.022$, $p = 0.049$). In female offspring rats of 10 HI group, EPA metabolite (14,15-DiHETE) was correlated with BDNF expression in cerebellum as well ($r = 0.057$, $p = 0.000$) (Fig. 4B and C).

4. Discussion

The World Health Organization (WHO) suggests a daily consumption of 150 μg of iodine to guarantee an adequate TH production, and recommends approximately 250 μg iodine intake daily for pregnant and lactating women [17,18]. In our previous study, Wang et al. demonstrated that Wistar rats received normal diet and deionized water in the normal iodide intake group. Therefore, the intake of iodide was 7.5 μg/day [19]. Liang et al. reported that pregnant Wistar rats in normal iodide intake group consumed deionized water and a normal diet, resulting in daily iodide intake of 7.5 μg/d [16]. Wang et al. demonstrated that the rats in normal iodide intake group received dietary feed containing iodide (7.5 μg/day), in addition to orally administered deionized water [20]. Liu et al. reported that the rats in normal iodide intake group received dietary feed containing iodide (7.5 μg/day), in addition to the oral administration of deionized water [10]. So we determined 7.5 μg as the overall daily iodine intake of rats in NAI group. In this experimental design, the iodide intake in rats of NAI (7.5 μg/d) group results equivalent to a daily consumption dosage of 150 μg of iodine in adult. A daily consumption dosage of 250 μg of iodine in pregnant women is 1.67 times as much as a daily consumption of 150 μg of iodine in adults. So we determined 12.5 μg/d as the iodide intake in rats of NPI group.

We showed that high iodide intake (5 HI and 10 HI) during pregnancy and lactation until PN16 can elevate FT3, FT4 levels in maternal and offspring rats. Pregnant women, breastfeeding women, and children are particularly affected by iodine [21]. Iodine excess establishes a status of excessive thyroid hormone synthesis and release, which contributes to the development of iodine-induced hyperthyroidism in iodine abundant areas [22].

We demonstrated that the increased FT3 in high iodide intake rats may stimulate the expression of TRα, TRβ, KLF9 and BDNF in brain. Besides, we showed positive staining for KLF9 is co-localized with TRβ in blood cells within microvessels, in neurons of hippocampus, in choroid plexus, and in Purkinje cells of cerebellum, which suggest that the increased FT3 acts directly on KLF9 in the brain by binding to TR. The expression of KLF9 in the developing rat brain depends on thyroid status in a T3-dependent manner. Avci et al. reported T3 is a key factor to determine the time at which Purkinje cells lose their ability to regenerate their axons in organotypic cultures. This function of T3 is mainly mediated by TR and involves its downstream target KLF9 [23]. The induction of hypothyroidism in neonatal pups resulted in reduced expression of KLF9 [24]. Intraperitoneal injection of T3 increased the expression of KLF9 in the hippocampal region and cerebellum in mice [25]. Besides, KLF9 is necessary for neuronal maturation in the developing dentate gyrus and during adult hippocampal neurogenesis. Morita et al. showed clearly reduced activity levels in rotorod and contextual fear-conditioning tests in the KLF9$^{-/-}$ mutant mice due to defective functions of the hippocampus [26]. KLF9 is necessary for Purkinje cell survival in organotypic culture, and mediates TH-dependent inhibition of axonal regeneration in the cerebellum as well [27]. Brain-derived neurotrophic factor (BDNF) is a downstream effector of KLF9 signaling (BDNF), which plays an important role in neuronal survival, differentiation, and synaptic plasticity in the brain [28].

Moreover, we demonstrated that high iodide intake during pregnancy and lactation enhances DHA and EPA metabolites, especially in 5 HI group of offspring rats. It is known that iodine is critical for normal brain development. Pal et al. studied the effects of iodine supplementation on offspring rats of iodine-deficient maternal rats, found that iodine supplementation (10 mg iodine/20 g of diet) significantly improve the dendrite architecture in cerebellums, and TUNEL positive cells were decreased [29]. Brain structure and function depend on sufficient supply with DHA and EPA [30]. DHA and EPA are essential for fetus brain development during pregnancy and lactation [31], which has been implicated in learning and memory [32]. DHA administration during gestation and nursing has been reported to increase hippocampal dendritic spine density and some synaptic proteins in the brains of weanling rat pups [33]. EPA is associated with reduced risk of neuropsychiatric and neurodegenerative diseases. Kawashima et al. suggest that EPA protects against neurodegeneration by modulating synaptic plasticity and activating the PI3kinase/Akt pathway, possibly by its own functional effects in neurons and glial cells and by its capacity to increase brain DHA [34].

Furthermore, we found that serum EPA metabolite (9-HEPE) was significantly correlated with KLF9 expression, serum DHA metabolite (17-HDoHE) and EPA metabolites (15-HEPE, 17,18-EEQ and 14,15-DiHETE) were correlated with BDNF expression. It is reported that DHA can induce BDNF expression through a pathway involving p38MAPK in primary astrocytes [12]. Supplementation of DHA increased hippocampal expression of BDNF [35]. EPA may exert neuroprotective functions by up-regulating the expression of BDNF as well, because EPA can modify the activity of several membrane-bound enzymes, including protein kinase C, which is linked to BDNF transcription [36]. Peng et al. reported that hippocampal expression of BDNF was decreased in a chronic unpredictable mild stress-induced model of depression, which were reversed by EPA supplement [37].

However, excess iodine has the theoretical basis of impairing intelligence: excess iodine can induce hypothyroidism, which can cause mental retardation; in addition, more and more experiments in vitro and in vivo have found that excess iodine damaged nerve cells. Using Sprague-Dawley rats exposed to excess iodine from pregnancy to 6 months post-delivery as in vivo model, Cui et al. showed that excess iodine (5000 μg/L KIO_3) could change the hippocampal cell structure, activate the mitochondrial apoptosis pathway and damage the spatial learning and memory capacities in offspring of both genders [38]. Zhao et al. reported that the male offspring were given 5000 μg/L KIO3 from PN0 to 8 weeks of age, ecxess iodine treatment increased malondialdehyde accumulation, decreased superoxide dismutase activity and glutathione (GSH) level, and enhanced levels of autophagy markers in the hippocampus, including LC3, Beclin1, and p62, and impaired the learning and memory capabilities [39]. Liu et al. studied that a total of 1229 students aged between 8 and 10 years were recruited with a mean IQ of 105.8 in Tianjin, China, children who resided in regions with a very high water iodine concentration (234.7 μg/L), there was on average a reduction of IQ by nearly nine points in comparison with those who resided in a non-high water iodine area [40].

Some limitations have also been identified. First, it is not clear from the results of the study, whether this change in BDNF levels/synthesis and DHA and EPA metabolism is due to changes in the plasma levels of thyroid hormones. The results obtained should be considered as indicative not confirmative. Studies of better design, such as rats are injected with thyroid hormone, should be carried out to confirm the results obtained. Second, whether reduction in BDNF and EPA and DHA metabolites subsequent to iodine leads to hypothyroidism requires further investigation. We will study this limitations later.

In conclusion, we demonstrate that high iodide intake during pregnancy and lactation until PN16 elevates FT3 levels, stimulates KLF9, TRα, TRβ and BDNF expression in hippocampus and cerebellum, and enhances DHA and EPA metabolites in offspring rats, especially in 5 HI group. Correlations between serum EPA, DHA metabolites and KLF9, BDNF expression in brain are demonstrated. All these evidences suggest an insight for the essential role of DHA, EPA metabolites and thyroid response element KLF9 as well as BDNF expression in brain, which might be potential iodine status biomarkers following different iodide intake during pregnancy and lactation, and shed light on brain development in offspring.

Author contribution statement

Hailing Zhao: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Xiuxiu Zhao: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Yue Sun: Performed the experiments; Wrote the paper.

Xiaomei Yao: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Wanqi Zhang: Conceived and designed the experiments.

Funding statement

This work was supported by National Natural Science Foundation of China (nos. 81874257 and 82230113) as well as the Principal Investigators, Xiaomei Yao and Wanqi Zhang.

Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no conflicts of interest.

Acknowledgement

Thanks to the help from Large Research Equipment Sharing Platform in Tianjin Medical University.

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