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CHANGES IN PLASMA TRIIODOTHYRONINE, THYROXINE, AND THYROID-STIMULATING HORMONE AFTER ^{131}I IRRADIATION OF NEWBORN RATS FED WITH IODINE DEFICIENT DIET

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Abstract

Background: Human thyroid gland is generally regarded as a relatively low-risk organ in terms of developing radiation-induced tumorigenesis. However, a rapid increase in the incidents of thyroid cancer after the Chernobyl nuclear reactor accident in 1986 provided additional insight into the risk of thyroid cancer. Three key risk factors have been identified to be involved in this increase: (1) internal irradiation from ^{131}I fallout, (2) young age, and (3) a low-iodine diet. Our previous study demonstrated that the thyroid radiation dose was highest in the newborn rats fed with low-iodine diet when rats of varying ages were internally exposed to ^{131}I at the same radioactivity per body weight.

Objective: To examine the short-term effects of a low dose internal irradiation of ^{131}I on the status of the thyroid hormone in rats of three different ages maintained on either standard diet or low-iodine diet.

Methods: ^{131}I was injected intraperitoneally in F344 rats at the ages of 1, 4, and 9 weeks. Animals were maintained with an iodine-deficient (IDD) or a standard (SD) diet. Changes in serum levels of triiodothyronine (T_3), thyroxine (T_4), and thyroid-stimulating hormone (TSH) were examined.

Results: Dramatic changes in hormone levels were found only in the rats belonging to 1-week-old IDD group, in which T_3 levels rapidly dropped and TSH levels increased after ^{131}I irradiation, whereas they remained unchanged in the SD group. In 4- and 9-week-old rats, hormone levels were also steady after irradiation, with no differences between the IDD and SD groups.

Conclusions: These data suggest that under low-iodine conditions, the status of thyroid hormone of newborn rats is particularly sensitive to internal irradiation of ^{131}I.

Key words: triiodothyronine, thyroxine, I^{131} irradiation, iodine-deficient diet, newborn rats.

Резюме

ИЗМЕНЕНИЯ В ПЛАЗМЕ ТРИЙОДТИРОНИНА, ТИРОКСИНА И ТИРЕОТРОПНОГО ГОРМОНА ПОСЛЕ ОБЛУЧЕНИЯ ^{131} I У НОВОРОЖДЕННЫХ КРЫС, СОДЕРЖАВШИХСЯ НА ЙОДОДЕФИЦИТНОМ ПИТАНИИ

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Введение: Щитовидная железа человека обычно рассматривается как орган с относительно низким риском развития пострадиационного онкогенеза. Однако резкое увеличение случаев рака щитовидной железы после аварии на Чернобыльской АЭС в 1986 году создало предпосылки к изучению факторов риска развития рака щитовидной железы. Были определены три ключевых фактора риска: (1) внутреннее облучение от ^{131}I, (2) молодой возраст, и (3) диета с низким содержанием йода. Наше предыдущее исследование крыс различного возраста и массой тела, которые были подвержены облучению ^{131}I продемонстрировало, что самой высокой была доза облучения щитовидной железы у новорожденных крыс, содержащихся на диете с низким содержанием йода.

Цель: Исследовать кратковременные эффекты низкой дозы внутреннего облучения ^{131}I на состоянии гормона щитовидной железы у крыс трех различных возрастов, содержащихся на стандартной диете или на диете с низким содержанием йода.

Методы: ^{131}I был инъецирован внутрибрюшинно F344 крысам в возрасте 1, 4, и 9 недель. Животные содержались на диете с низким содержанием йода (НЗЙ) или на стандартной диете (СД). Были исследованы изменения в сыворотке крови трийодтиронина (Т3), тироксина (Т4) и тиреотропного гормона (TSH).

Результаты: Значительные изменения гормонального уровня были зафиксированы только у крыс, принадлежащих к группе в возрасте 1 неделя и содержащихся на диете с низким содержанием йода, так уровень Т3 гормона резко снизился, уровень TSH гормона после облучения увеличился, в то время как, в группе крыс, содержащихся на стандартной диете, уровень этих гормонов не изменился после облучения. Гормональные уровни у крыс в возрасте 4 и 9 недель были также устойчивы после облучения, без различий между группами крыс, содержащихся на диете с низким содержанием йода и группой крыс со стандартной диетой.

Заключение: Эти данные свидетельствуют о том, что при условиях йододефицита, статус гормона щитовидной железы новорожденных крыс особенно чувствителен к внутреннему облучению ^{131}I.

Ключевые слова: трийодтиронин, тироксин, ^{131}I облучение, диета с низким содержанием йода, новорожденные крысы.

Түйіндеме

ЙОДПЕН АЗ МӨЛШЕРДЕ ТАМАҚТАЛҒАН, ЖАҢА ТУҒАН ЕГЕУҚҰЙРЫҚТАРДА, ^{131} I СӘУЛЕЛЕНДЕРУ КЕЙІН, ПЛАЗМАДА ТРИЙОДТИРОНИН, ТИРОКСИН ЖӘНЕ ТИРЕОТРОПИН ГОРМОНДАРЫНЫҢ ӨЗГЕРУЫ

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Кіріспе: Адамның қалқанша безі, негізінде радияциядан кейін қатерлі ісікке шалдығу қаупі аз мүше болып саналады. Бірақ 1986 жылы болған Чернобылда АЭС-ның авариядан кейін , қалқанша бездің қатерлі ісіктердің күрт көбейгені анықталды. Соңдықтан қалқанша бездің қатерлі ісіктерді әсер ету факторларын зерттеу керек болды. Ұш негізгі кауіп факторлар анықталды: (1) ішкі сәулелендіру ^{131}I, (2) жасы, (3) дене салмағы. Алдында болған зерттеуде, ен көп радияцадан зардап алған жаңа тұған егеуқұйрықтар йодпен аз мөлшерде тамақталған.

Мақсаты: әр түрлі жастағы егеуқүйрықтарда, аз мөлшерде йодпен тамақталған, қалқанша бездің гормондарына ішкі сәулелендерудің аз дозаларының қысқа мерзімді әсерін зерттеу керек.

Әдістер: 1, 4, 9 апталық F344 егеуқүйырықтар іштеріне ^{131}I салынған. Жануарлар йодпен аз мөлшерде тамақталған. Қан сарысуында трийодтиронин (Т3), тироксин (Т4) және тиреотропты гормон (TSH) анықталған.

Нәтижелер: Гормондардың манызды өзгертулері, 1 апталық егеуқүйырықтарда анықталды, Т3 денгейі тез төмендеді, TSH денгейі өзгерген, ал басқа топтарда осы гормондар өзгерген жоқ.

Қортынды: Йодтапшылығы бар жаңа тұған егеуқұйрықтарда қалқанша без ішкі сәулелендеруге сезімтал ^{131}I.

Негізгі сөздер: трийодтиронин, тироксин, ^{131}I сәулелендеру, иодпен аз мөлшердегі диета, жаңа тұған егеуқұйрықтар.

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Фуджимото Н., Нитта Ю., Ендо С., Хоши М. Йодпен аз мөлшерде тамақталған, жаңа туған егеуқұйрықтарда, ^{131} I сәулелендеру кейін, плазмада трийодтиронин, тироксин және тиреотропин гормондарының өзгеруы / / Ғылым және Денсаулық сақтау. 2016. №3. Б. 26-33.

Introduction

Iodine deficiency is thought to be a risk factor for thyroid cancer [1-4]. In fact, administration of an iodine-deficient diet (IDD) soon leads to thyroid hyperplasia accompanied by low serum thyroxine (T_4) and high thyroid-stimulating hormone (TSH) levels, and in rodents, thyroid adenomas subsequently develop [5, 6]. When combined with exposure to a chemical carcinogen, the latency of the development of a thyroid tumor is shortened by IDD [7].

A number of studies have demonstrated that ionized radiation can cause thyroid cancer, although there is some controversy regarding the dose–response relationship in animal models. Potter *et al.* [8] and Doniach [9] concluded that external X-ray irradiation is about 10 times more effective that internal ^{131}I exposure for the induction of thyroid tumors in rats. Other reports indicated an equal sensitivity to both [10, 11]. The human thyroid gland is generally regarded as having a relatively low risk of developing radiation-induced tumorigenesis, because observations in pediatric patients treated with ^{131}I for various thyroid disorders have indicated no thyroid cancer risk at doses of <600 rad [12]. An additional study of the risk of thyroid cancer after diagnostic doses of ^{131}I also concluded that the thyroid has a low-carcinogenic potential [13]. Subsequently, the nuclear reactor accident in Chernobyl in 1986 provided further insights into the risks of thyroid cancer. After the accident, the number of children suffering from thyroid cancer increased dramatically in radiation-contaminated regions [14-16]. This rapid increase in the number of cases of pediatric thyroid cancer within a few years of exposure to radioactive isotopes was unexpected. The following three key risk factors have been implicated in the rapid increase in thyroid cancer incidence across the affected

areas: (1) ^{131}I fallout from nuclear reactors is a particularly strong inducer of thyroid cancer, (2) the incidences of thyroid carcinoma in children under the age of 15 years was markedly increased compared with adults, and (3) a relatively low-iodine diet in the affected areas than in unaffected areas [17, 18]. In our previous study, we investigated the short-term effects of a low dose internal irradiation of ^{131}I using rats of varying ages maintained on standard (SD) and IDD diet. We found that the dose of thyroid radiation was higher in rats fed with IDD diet than in rats fed with SD diet. In addition, the higher thyroid doses were noted in 1-week-old rats than in older rats [19]. In this study, we measured serum triiodothyronine (T_3), T_4, and TSH levels of the serum samples of our previous study focusing on the effect of IDD and age.

Materials and Methods

Diet

The SD and IDD were purchased from Oriental Yeast Co. Ltd., Tokyo. The SD contained 0.92 ppm of iodine, whereas the IDD contained only 0.04 ppm. The standard tap water contained 20–50 ppm of iodine. Purified Milli-Q water (Millipore Japan, Tokyo, Japan) that was provided to the IDD groups contained 0.13 ppb of iodine.

Animal experiments

The animal experiments have been previously described [19]. Briefly, F344 3- and 8-week-old female rats were purchased from Charles River Japan Inc. (Atsugi, Japan). Newborn rats were obtained by random mating of F344 rats from the same company. Half of the animals at each age were maintained with free access to SD and tap water, whereas the rest were administered IDD and Milli-Q water from 1 week prior to the ^{131}I injection (i.e., administration started at ages 0, 3, and 8 weeks) to the end of the experimental period. The mothers were provided the diet and the water in 1 week-old groups. The experimental facility was air-conditioned, maintaining an ambient temperature of 24 ± 2 °C a relative humidity of 55 ± 5% with a 12 h light/dark cycle. All animal experiments were conducted following the guidelines set out by Hiroshima University in the "Guide for the Care and Use of Laboratory Animals."

Single doses of Na^{131}I (Daiichi Pure Chemical Co. Ltd., Tokyo, Japan) at 103 kBq per 100 g body weight were injected intraperitoneally at the ages of 1, 4, and 9 weeks. Animals were sacrificed under ether anesthesia at 0, 0.25, 0.5, 1, 2, 4, 8, and 16 days after the injection. Blood samples were collected and serum samples were stored for hormone assays.

Hormone assays

Total T_3 and T_4 were determined using Amarex-MT3 and Amarex-MT4 radioimmunoassay kits, respectively (Oso Clinical Diagnostic Co, Tokyo, Japan). The TSH concentration of Serum was measured by radioimmunoassay using NIDDK reagents (NIDDK-rTSH-RP-2 as the reference) following the recommended protocol [20]. The antigen was iodinized using the lactoperoxidase method. The second antibody, anti-rabbit IgG, was kindly provided by the Institute of Molecular and Cellular Regulation, Gunma University.

Statistical analyses

Statistical comparisons were conducted using ANOVA followed by Scheffe's test.

Results

Animals

Animals in all groups remained healthy during the 2-week experimental period after irradiation. The body weights steadily increased. There were no significant differences in thyroid as well as body weights between the SD and IDD groups.

Serum T_3 and T_4

Figures 1 and 2 show time-dependent changes in the serum T_3 and T_4 levels after the injection of ^{131}I.

The most dynamic changes occurred in the rats belonging to the 1-week-old IDD group with the T_3 levels significantly dropping between 6 and 48 h and then returning to the initial level. However, in the rats belonging to the 1-week-old SD group, serum T_3 levels remained constant throughout the experimental period. In both 1-week-old groups, the serum T_4 levels decreased at 12 h, following which the levels were raised significantly above the initial level between days 4 and 8.

Serum TSH levels

On days 2–4, significantly elevated serum TSH levels were noted in the rats belonging to the 1-week-old IDD group. In both groups, in 4- and 9-week-old rats, the hormone levels fluctuated to some degree during the first 24-h period after the ^{131}I injection; however, they subsequently stabilized, without any significant differences between the IDD and SD treated groups.

Fig.1

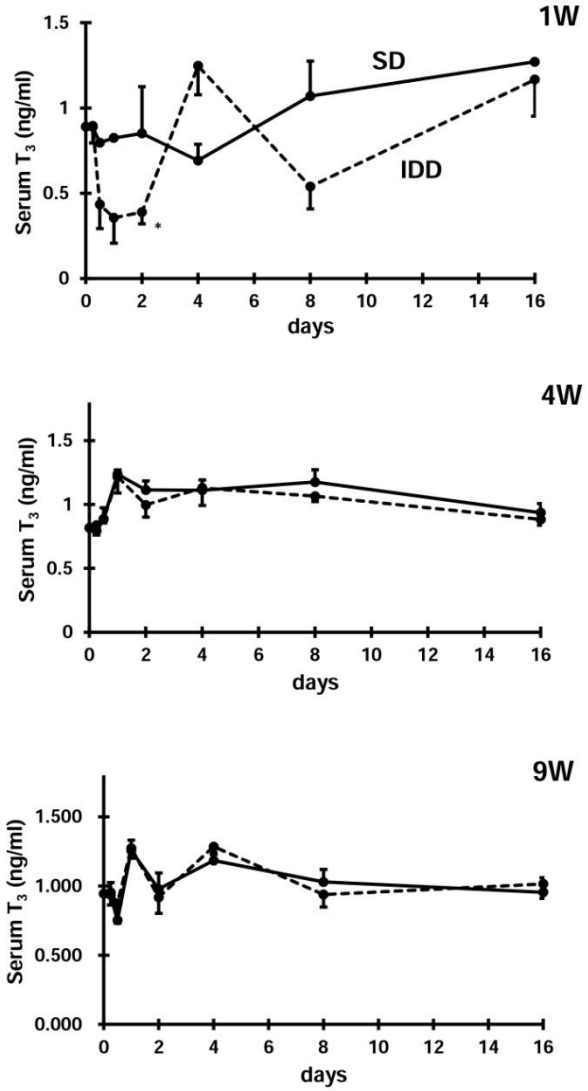

Fig. 1. Time-dependent change in serum triiodothyronine (T_3) after an injection of ^{131}I (bars indicate standard error of the mean (SEM); *significant difference from the initial value at $p < 0.05$, n = 3).

Fig.2

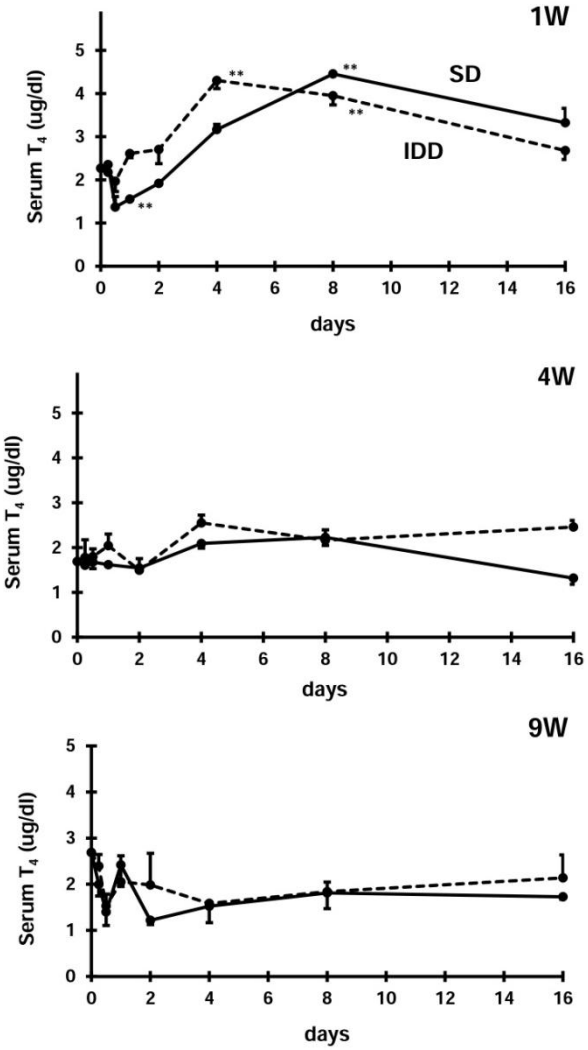

Fig. 2. Time-dependent change in serum thyroxine (T_4) after an injection of ^{131}I (bars indicate standard error of the mean (SEM); **significant difference from the initial value at $p < 0.01$, n = 3).

Discussion

This study, conducted using rats aged 1, 4, and 9 weeks, demonstrated that the thyroid function is sensitive to irradiation in 1-week-old animals under low-iodine diet.

Thus, the ^{131}I injection resulted in temporary interruption in serum T3 levels and an increase in serum TSH levels.

Our previous study measuring the radiation doses as a function of thyroid weight over 16 days demonstrated the following: (1) the thyroid radiation doses were higher in the IDD than SD groups, independent of age and; (2) the highest thyroid radiation doses were noted in 1-week- old rats in both the IDD and SD groups. Consequently, the thyroid radiation doses were the highest in the 1-week-old IDD group, followed by the 1-week-old SD, which could be involved in differential changes in thyroid hormones as well as TSH in 1-week-old group.

The effects of age on ^{131}I metabolism in the thyroid gland of rats were previously examined by Sikov [21]. The uptake and retention of ^{131}I were found to be age-specific, with maximal levels being higher in adults than in young animals.

Fig.3

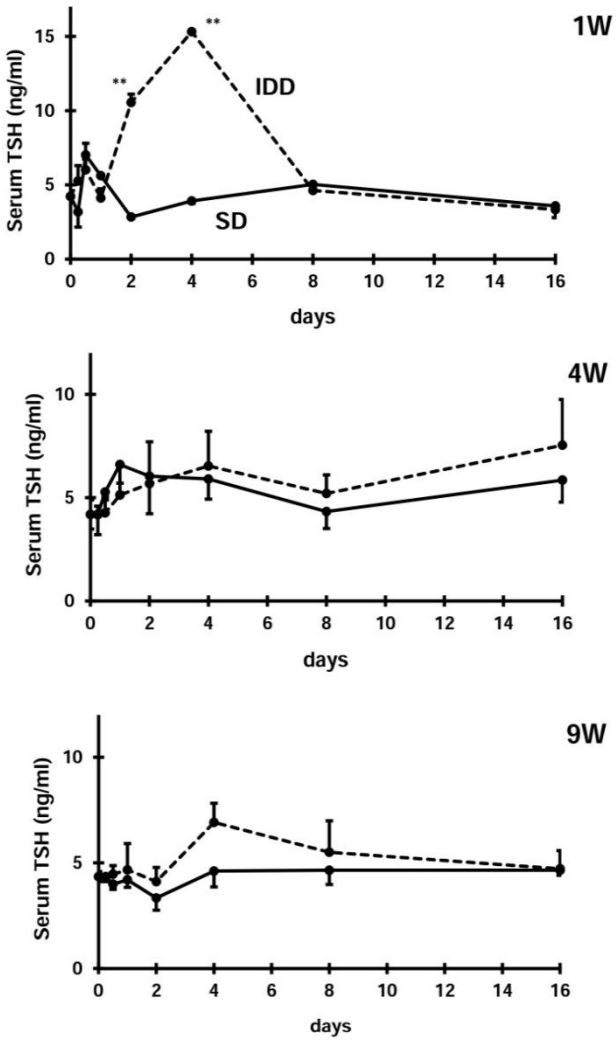

Fig. 3. Time-dependent change in serum thyroid-stimulating hormone (TSH) after an injection of ^{131}I (bars indicate standard error of the mean (SEM); **significant difference from the initial value at p < 0.01, n = 3).

After examining the nature of the acute morphological response in rats of different ages, Sikov concluded that the retention curves generally reflected damage to the thyroid glands, with this damage reducing retention of ^{131}I, with relatively radio-resistant function in adults. However, this conclusion was based on the experiments of rats exposed to ^{131}I at levels of >1,800 kbq/100 g body weight. In this study, the injected radioactivity was 103 kbq/100 g body weight, which did not cause any severe damage to the thyroid gland. The radiation-induced atrophy in the thyroid tissue appeared minor, and the changes were transient [19]. IDD treatment increased the uptake as well as retention of ^{131}I in the gland, particularly in 1-week-old rats. The growth of thyroid follicles during the infancy would account for the higher retention, because thyroid accumulates iodine with increasing size of the follicles.

When ^{131}I was injected, rats had been treated with IDD for a week, and there were no differences in serum levels of T_3, T_4, or TSH from the SD groups. These results agree with Fukuda *et al.* [5], who reported that continuous feeding of a low-iodine diet results in a decrease in serum thyroid hormone levels; however, these decreases did not occur within a week. In rats, development of the hypothalamus–pituitary–thyroid axis occurs during the neonatal period. T_4 rises to peak concentrations at between 12 and 20 days of age, whereas the peak in T_3 is delayed until 20–32 days of age [22, 23]. The gradual increase in T_4 noted in 1-week-old group may be the consequence of the normal development of T_4 production. However, T3 levels in the 1-week-old rats of IDD group were unstable, with decreases observed on day 2, increases on day4, and no significant changes subsequently. The serum TSH levels changed accordingly. In 4- and 9-week-old rats, the thyroid hormones and TSH levels were steady during the experimental period, except for some minor changes on the first day.

In rats, the disturbance of the development of the hypothalamus–pituitary–thyroid axis during the neonatal period can cause permanent impairment of function. Thus, when hypothyroidism was induced in the rats by T_4 injection during the first 10 days of neonatal life, the T_4 levels remained at two-thirds of the control value for the rest of their lives, with TSH production also being affected [24, 25]. The effects of iodine deficiency on the development of thyroid function during the neonatal period have not been experimentally elucidated in detail; however, a previous study has shown that maintaining newborn rats on a low-iodine diet for the first 7 weeks of life resulted in a decrease in the growth rate after weaning, although plasma TSH levels were the same as in rats maintained on a standard diet [26].

A large-scale experiment with 6-week-old female Long-Evans rats exposed to ^{131}I concluded that the 2-year risk of the development of a thyroid tumor occurs at ^{131}I levels between 0.9–2.3 × 10^{-4}/rad, without a clear threshold [11].

According to our study, the dose of ^{131}I used in the investigation should substantially increase the risk of thyroid carcinogenesis. Dramatic effects of ^{131}I exposure on the hormone levels were observed in the neonatal rats under iodine-deficient conditions. Whether this could lead to permanent effects, including an increase in the susceptibility to thyroid carcinoma, remains to be investigated.

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