The Effect of Small Increases in Dietary Iodine on Thyroid Function in Euthyroid Subjects

T. Paul, B. Meyers, R.J. Witorsch, S. Pino, S. Chipkin, S.H. Ingbar, and L.E. Braverman

Dietary iodine intake in the United States is greater than that considered necessary for the maintenance of normal thyroid function. The administration of pharmacologic quantities of iodine (10 to 1,000 mg daily) to euthyroid subjects results in small decreases in the serum T_4 and T_3 concentrations and a compensatory increase in the basal and TRH-stimulated serum TSH concentrations. Studies were carried out to determine whether a far smaller increase in iodine intake would also affect thyroid function. Normal volunteers received 1,500, 500, or 250 μg supplemental iodine daily for 14 days. Following the administration of 1500 μg iodine daily, there were small but significant decreases in the serum T_4 and T_3 concentrations and a small compensatory increase in the serum TSH concentration and the serum TSH response to TRH. In contrast, no changes in pituitary-thyroid function occurred during the administration of 500 or 250 μg iodine daily. These findings indicate that a small increase in dietary iodine can induce subtle changes (all values remaining within the normal range) in pituitary-thyroid function, probably by inhibiting thyroid hormone release. The smaller iodine supplements of 500 and 250 μg daily, quantities that may easily be achieved under normal conditions, did not, however, affect thyroid function.

IN BOTH rat[1] and man,[2] the acute administration of sufficient quantities of iodine results in a transient inhibition of the intrathyroid organification of iodide and subsequent thyroid hormone synthesis. This response has been termed the acute Wolff-Chaikoff effect and depends upon the establishment of a high concentration of inorganic iodide within the thyroid, rather than the plasma.[3] Despite continued iodine administration,[4] thyroid hormone synthesis resumes, a phenomenon termed the escape from, or adaptation to, the acute Wolff-Chaikoff effect. It is clear that escape or adaptation in the rat is due to a decrease in the activity of the thyroid iodide transport mechanism, which lowers levels of intrathyroid iodide below that necessary to maintain inhibition of hormone biosynthesis.[3,5] A second major effect of iodine on the thyroid is inhibition of the proteolytic mechanisms necessary for hormone release. This effect is most clearly evident in patients with hyperthyroidism[6] but also occurs in euthyroid subjects.[7]

We and others have reported that pharmacologic doses of iodine (up to 1,000 mg daily) administered for 1 to 11 weeks to normal, euthyroid volunteers almost always results in small but significant decreases in serum T_4 and serum T_3 concentrations and compensatory increases in both basal serum TSH concentrations and the responses elicited by the administration of thyrotropin releasing hormone (TRH).[8-13] It is likely that these subtle changes in pituitary-thyroid function are due to the inhibitory effect of excess iodine on thyroid hormone release, and that the compensatory increase in TSH secretion prevents a further decline in plasma thyroid hormone concentrations, thereby maintaining them within the normal range.[8]

In the present study, we have evaluated the effects of much smaller quantities of iodine on thyroid function in normal volunteers. The study was undertaken for several reasons. First, iodine intake has increased in recent years in the United States. Whether or not such increases in iodine intake may have affected thyroid function in subjects without underlying thyroid disease is unclear. Second, many individuals ingest dietary supplements, such as kelp or multivitamin preparations; these contain more, sometimes much more, than enough iodine to fulfill the minimum daily requirement of approximately 150 μg iodine. When added to the usual dietary sources of iodine, they result in daily intakes well in excess of the norm. Finally, we have recently reported that the ingestion of huge quantities (200 mg/d for 14 days) of the iodine-rich food colorant, 2',4',5',7'-tetraiodofluorescein (erythrosine) resulted in small increases in both basal and TRH-simulated serum TSH concentrations similar to those that follow ingestion of pharmacologic quantities of iodine.[14] This resulted in an increase in daily urinary iodine excretion of approximately 1,200 μg. For these reasons, we evaluated the effects of small increments in iodine intake (1,500 μg daily), thereby determining whether the alterations in TSH secretion induced by erythrosine were due to the dye itself or could have been due to the iodide liberated thereof. Even smaller doses of iodine (500 and 250 μg) were also given to normal subjects to determine whether these physiologic supplements would affect thyroid function.

MATERIALS AND METHODS

Protocols

Nine euthyroid men between the ages of 26 and 56 years (34 ± 3, mean ± SE) and 23 euthyroid women between the ages of 23 and 44

From the Division of Endocrinology and Metabolism, Department of Medicine, University of Massachusetts Medical School, Worcester, MA; the Department of Physiology, Medical College of Virginia, Richmond, VA; and the Charles A. Dana Research Institute and the Harvard Thorndike Laboratory of Beth Israel Hospital, Department of Medicine, Beth Israel Hospital and Harvard Medical School, Boston.

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Address reprint requests to L.E. Braverman, MD, Division of Endocrinology and Metabolism, Department of Medicine, University of Massachusetts Medical School, Worcester, MA 01605.

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years (32 ± 2) were studied. Careful history and physical examination revealed no evidence of thyroid disease in any, and none had detectable quantities of antithyroid antibodies. A 24-hour urine was collected for baseline urinary iodine (I) and creatinine (Cr) excretion. Urinary creatinine was measured to help assure that the 24-hour urine collection was complete. At 9 AM on day 0, an indwelling venous catheter was inserted into an antecubital vein and blood collected for baseline serum protein bound (PBI) and total iodine (TI), thyroxine (T_4), triiodothyronine (T_3), and thyrotropin (TSH) concentrations, as well as for determinations of the resin T_3 uptake and free T_4 index (FT_4I). Thyrotropin releasing hormone (TRH, 500 μg, Relefact, Hoechst-Roussel, Somerville, NJ) was then administered as a bolus through the intravenous catheter, and blood was obtained 15, 30, 45, and 60 minutes later for the measurement of serum TSH concentrations. All subjects were then treated with various doses of iodine in 0.5 mL of water po (NaI and 5 mg ascorbic acid/mL) every 12 hours for the following 14 days. The men received 750 μg iodide twice daily and the women received 750, 250, or 125 μg twice daily. Some of the women were studied at two dose levels at least one year apart. A 24-hour urine collection was obtained for measurement of I and Cr content on day 7, and at 9 AM on day 8, prior to iodine ingestion, a sample of blood was obtained for serum iodine analyses. Another 24-hour urine specimen was collected on day 14 and the TRH test repeated at 9 AM on day 15, as outlined above.

Five additional age-matched men were studied as outlined above, but were not given the iodine supplement. No changes in serum T_4 and T_3 concentrations, the FT_4I, and basal and TRH stimulated serum TSH concentrations were observed in these five volunteers during the 14-day study period.

Methods

Samples of serum and urine were frozen at −20°C until analyzed. All measurements were made in duplicate and all serum samples for a given test were assayed in the same assay. Serum T_4, T_3, and TSH concentrations were measured by radioimmunoassay (ARIA-HT, Beetin Dickinson Immuno Diagnostics, Orangeburg, NY) and the FT_4I was calculated as the product of the total T_4 and the T_3 resin uptake (ARIA). Normal ranges for these thyroid function tests are: T_4 (4.3 to 9.5 μg/dL); FT_4I (4.4 to 9.4); T_3 (100 to 205 ng/dL); TSH (0.5 to 5 μU/mL). Antithyroglobulin (anti-Tg) and antimicrosomal (anti-M) antibodies were measured by a tanned red blood cell technique (Ames Division, Miles Laboratories, Elkhart, IN). Serum PBI and TI and urine I concentrations were measured by the method of Benotti et al[15] and urine Cr by antoanalyzer. The serum inorganic iodide concentration was calculated as the difference between the TI and PBI concentrations. The 24-hour urinary I excretion is reported as μg I/24 h.

Statistics

All values are reported as the mean ± SE and statistical significance of differences observed was assessed by the Student's paired *t*-test.

RESULTS

Urine and Serum Iodine

In the men and women receiving 1,500 μg iodine daily, the mean 24-hour urine I excretion increased from 211 ± 41 μg I/24 h on day 0 to 1,360 ± 74 on day 7 ($P < .001$) and 1,308 ± 58 on day 14 ($P < .001$). The increase in I excretion approximated the quantity of additional iodine administered, confirming subject compliance. Losses of iodine in the feces, sweat, salivary glands, choroid plexus, and gastric mucosa could not be evaluated. In these subjects, the increase in iodine intake induced a small, but significant, increase in serum TI concentrations from baseline values of 5.9 ± 0.2 μg/dL to 7.6 ± 0.4 on day 8 and 7.6 ± 0.4 on day 15. Since the serum PBI did not change, calculated values of the serum inorganic I concentration increased significantly, from baseline values of 0.7 ± 0.1 μg/dL to 2.4 ± 0.3 on day 8 ($P < .01$) and 2.7 ± 0.4 on day 15 ($P < .01$).

The mean 24-hour urine I excretion in the women receiving 500 μg iodine daily increased significantly from 177 ± 21 μg daily to 410 ± 36 μg on day 8 and 506 ± 33 μg on day 15. In the women receiving 250 μg iodine daily, 24-hour urine I excretion also increased significantly from 186 ± 37 μg daily to 332 ± 28 μg on day 8 and 314 ± 39 μg on day 15. There was no change in serum TI, PBI, and inorganic I concentrations during administration of these two doses of iodine.

Serum Thyroid Hormone and Basal TSH Concentrations

Ingestion of 1,500 μg iodine daily induced small but significant decreases in the serum T_4 and T_3 concentrations and in values of the FT_4I and a significant increase in the TSH concentration on day 15. The administration of 500 μg or 250 μg iodine daily did not significantly affect the serum T_4, T_3, and TSH concentrations or the FT_4I (Table 1).

The maximum increment in the serum TSH concentration following TRH administration was significantly greater in both men and women receiving 1,500 μg iodine daily, compared with that observed on day 0 (Fig 1). The increase in the TSH response to TRH was also highly significant when integrated TSH responses (μU/mL × min) over one hour were calculated (men, 534 ± 49 *v* 752 ± 58, $P < .001$; women, 1,244 ± 112 *v* 1,653 ± 202, $P < .02$). The serum TSH response to TRH was significantly greater in the women than in the men, both before and during iodine administration ($P < .01$).

The administration of 500 μg iodine daily to nine women or 250 μg iodine to another nine women did not significantly affect the serum TSH response to TRH (Table 2).

Table 1. Effect of Iodine Ingestion for 14 Days on Thyroid Function Tests in Normal Volunteers

Daily Dose of Iodine	n	Serum T_4 (μg/dL)		Serum FT_4I		Serum T_3 (ng/dL)		Serum TSH (μU/mL)	
		Day 0	Day 15	Day 0	Day 15	Day 0	Day 15	Day 0	Day 15
1,500 μg	18	7.3 ± 0.2	6.7 ± 0.2*	7.0 ± 0.2	6.4 ± 0.2*	181 ± 4	173 ± 4†	1.9 ± 0.2	2.8 ± 0.4‡
500 μg	9	7.8 ± 0.4	7.9 ± 0.6	7.1 ± 0.3	7.1 ± 0.3	148 ± 5	144 ± 4	2.1 ± 0.3	2.4 ± 0.4
250 μg	9	7.9 ± 0.4	7.5 ± 0.3	7.6 ± 0.3	6.9 ± 0.2	134 ± 3	135 ± 4	2.3 ± 0.4	2.7 ± 0.5

Values are mean ± SE.

*$P < .001$.

†$P < .02$.

‡$P < .01$.

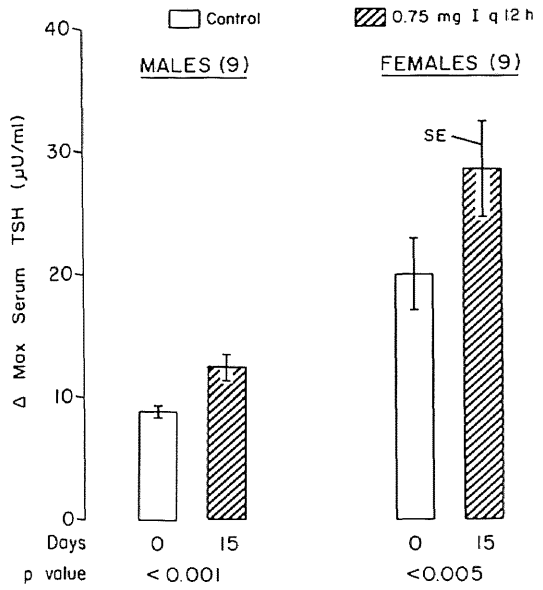

Fig 1. The effect of iodine administration on the maximum increase in the serum TSH concentration following the intravenous administration of 500 μg TRH. The numbers in parentheses represent the number of euthyroid subjects in each group. Statistical significance was determined by the Student's paired *t*-test.

DISCUSSION

Previous studies have clearly demonstrated that the administration of large iodine supplements (10 to 1,000 mg daily) to normal subjects for 1 to 11 weeks results in a small increase in both basal serum TSH concentrations and the TSH response to TRH, sometimes in association with decreased serum concentrations of T_4 and T_3.[8-13] These effects are almost certainly due to an inhibition by iodine of thyroid hormone release, with a compensatory increase in TSH secretion that may limit or forestall a further decline in serum T_4 and T_3 concentrations. In the present studies, we have shown that virtually identical changes are brought about by the administration of much smaller iodine supplements, ie, 1.5 mg daily. It is unlikely that this effect can be ascribed to an inhibition of hormone synthesis, since the Wolff-Chaikoff effect is normally quite transient and since the administration of even large doses of antithyroid agents does not result in the prompt decline in the serum T_4 concentration observed in the present study.

The similarity between the changes in pituitary-thyroid function noted here and those that follow the ingestion of huge quantities of erythrosine (200 mg daily),[14] and the close comparability of values of urinary iodine excretion in the two studies, strongly indicate that the subtle functional alterations seen in volunteers ingesting erythrosine were due to the iodine made available by the dye, either as a contaminant or by deiodination, rather than a direct effect of the dye itself on the thyroid or pituitary.

In the present study, no significant changes in pituitary-thyroid function were observed in the normal women receiving 500 or 250 μg iodine daily. This strongly suggests that such small increases in iodine intake, which may occur under normal conditions, do not affect thyroid function, at least in the short term.

The present and previous studies raise important questions concerning the effects of iodine on thyroid hormone economy. First, it is uncertain whether the subtle changes in pituitary-thyroid function that are caused by small iodine supplements (1,500 μg) would be sustained during longer periods of administration. Second, it is unclear whether such changes, even if sustained, would have significantly adverse consequences, especially in view of the fact that all values for thyroid-related hormones remained well within the normal ranges.

There is, in addition, a remarkable paucity of data concerning the long-term effects of the administration of truly pharmacologic doses of iodine to euthyroid subjects. In most studies, iodine was administered for approximately 2 weeks. In one prospective study, 1,000 mg iodine was given daily to four volunteers for 11 weeks.[13] This produced small changes in thyroid function, similar to those described here. These investigators also studied 37 patients with chronic lung disease treated with 1,000 to 2,000 mg iodine daily for a mean period of 2.2 years. Thirteen patients were biochemically hypothyroid and thyroid function returned to normal in seven of the patients following iodine withdrawal. The presence of autoimmune thyroiditis was not excluded in these patients, however. Autoimmune thyroiditis is associated with extrinsic asthma[16] and, as noted below, enhances the susceptibility to the development of iodine-induced hypothyroidism. Finally, we have recently reported that the ingestion of approximately 3 mg iodine daily for six months during daily mouth-rinsing with an iodine containing mouthwash did not effect thyroid function.[17]

Beyond question, there are, however, groups of susceptible individuals in whom levels of iodine intake that are well-tolerated by normal persons induce clear adverse effects. In patients with autonomously functioning thyroid tissue, very small doses of iodine in areas of iodine deficiency and higher doses in areas of iodine sufficiency, can induce hyperthyroidism.[18] Conversely, in some patients with Hashimoto's disease, Graves' disease treated with ^{131}I or surgery, or cystic fibrosis, and in patients who have undergone hemithyroidectomy, moderate to large increments in iodine intake can lead to the development of hypothyroidism.[18] Within this context, it is difficult to define an upper limit of normal for the daily iodine intake. It is perhaps preferable to consider the prob-

Table 2. The Effect of 500 μg or 250 μg Iodine Administered Daily to Euthyroid Women on the TSH Response to TRH

Daily Dose of Iodine	n	Δ Max Serum TSH (μU/mL)		Integrated Serum TSH Response (μU/mL × min)	
		Day 0	Day 15	Day 0	Day 15
500 μg	9	18.4 ± 2.8	20.7 ± 2.8	975 ± 151	1,088 ± 159
250 μg	9	19.1 ± 3.9	21.6 ± 5.8	1,008 ± 196	1,170 ± 298

Values are mean ± SE.

lem in terms of what is normal, what is acceptable, and what is clearly excessive. A usual iodine intake can be thought of as one that is commonplace in a given region and is not associated with an increased frequency of thyroid disease. An acceptable level of iodine intake would be one that is unusually high, but is also an uncommon cause of thyroid disease, whereas an excessive iodine intake would be one that leads to definite thyroid disease in a significant fraction of the population. From this standpoint it should be recognized, however, that what is acceptable for some patients is excessive for others, and vice versa.

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