EFFECT OF INCREASED IODINE INTAKE ON THE THYROIDAL RESPONSE TO TSH STIMULATION

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The thyroidal response to TSH is an established test of thyroid function. The thyroidal radioactive iodine (RAI) uptake is the most useful measure of this response (*1,2*). Iodine depletion increases the RAI uptake (*3,4*) and increases the thyroidal response to thyrotropin (TSH) (*5*) while iodine excess decreases the RAI uptake (*3,4,6*) and may decrease the response to TSH (*7,8*). There is wide geographic variation in iodine intake and increasing iodine intake with changing methods of food preparation (*4,6,9,10*). It would be of interest to know the effect of increased iodine intake on the response of the RAI uptake to TSH stimulation.

This study is a comparison of the response to TSH stimulation of subjects living in Southern California who have relatively high iodine intakes with a previously reported group of subjects from Alabama with lower iodine intakes (*1,10*).

METHODS AND MATERIALS

Fifty-seven euthyroid subjects were studied. None had evidence of endocrine, cardiac, hepatic, or renal disease. None were known to be receiving hormones or iodides or had previously received iodine-containing radio-contrast media. None were critically ill and all were eating a random diet. Each had a PBI in the normal range for our laboratory of 3.4–8.2 μg/100 ml (*11*). Sixty-six patients with primary hypothyroidism and 19 patients with hypothyroidism due to pituitary failure were studied for comparison. Twenty-four-hour ^{131}I uptake measurements were made at a distance of 35 cm from a 2-in. crystal with a flat-field collimator. Tissue background was counted over the thigh. The standard was measured in an ORINS thyroid phantom at the most superficial level. After the pre-TSH uptake, each subject received either 5 USP units of bovine TSH intramuscularly once or 10 units daily for 3 days. Eighteen hours after the final injection of TSH, background counts were obtained and a larger tracer dose of ^{131}I for the post-TSH 24-hr thyroidal uptake was administered (*1*). The significance of the difference of means was determined by Student's t-test. Regression analyses were performed by standard statistical methods (*12*). The mean intake of stable iodine was calculated from the 24-hr RAI uptakes by the method of Oddie, et al (*4*).

RESULTS

Euthyroid patients. The calculated mean iodine intake (*4*) was 359 μg/day for the 40 euthyroid Alabama subjects and 1,260 μg/day for 55 of the 57 euthyroid Southern California subjects. The 24-hr RAI uptakes before TSH stimulation (pre-TSH), the 24-hr RAI uptakes after stimulation (post-TSH), and the increments in 24-hr uptake for the euthyroid

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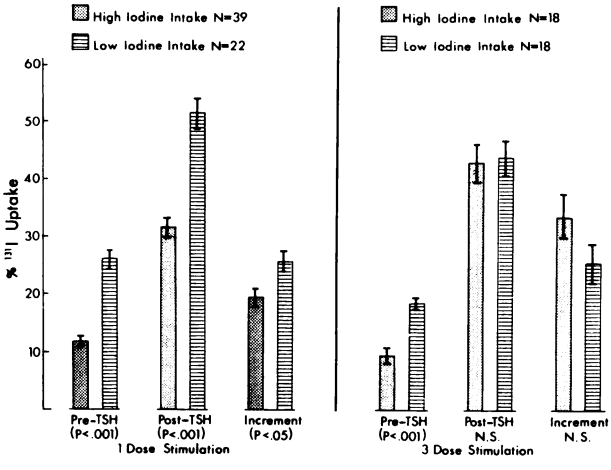

FIG. 1. Comparison of pre-TSH uptake, post-TSH uptake, and increment in uptake in two groups of euthryroid subjects with different levels of iodine intake.

TABLE 1. 24-HR THYROIDAL ^{131}I UPTAKE BEFORE AND AFTER ONE DOSE OF TSH IN 39 EUTHYROID PATIENTS

Pre-TSH (%)	Post-TSH (%)	Increment	Pre-TSH (%)	Post-TSH (%)	Increment	Pre-TSH (%)	Post-TSH (%)	Increment
12	35	(23)	22	34	(12)	3	19	(16)
19	44	(25)	7	30	(23)	16	30	(14)
15	26	(11)	13	25	(12)	10	23	(13)
23	76	(53)	7	13	(6)	6	21	(15)
12	51	(39)	14	25	(11)	14	32	(18)
24	40	(16)	10	52	(42)	7	30	(23)
13	25	(12)	11	30	(19)	8	18	(10)
5	30	(25)	10	30	(20)	5	19	(14)
12	28	(16)	19	33	(14)	19	30	(11)
11	38	(27)	18	34	(16)	7	30	(23)
3	17	(14)	15	37	(22)	25	40	(15)
4	24	(20)	9	16	(7)	5	37	(32)
15	25	(10)	10	49	(39)	3	31	(28)
			Mean 11.8	31.5	(19.7)			

TABLE 2. 24-HR THYROIDAL ^{131}I UPTAKE BEFORE AND AFTER THREE DOSES OF TSH IN 18 EUTHYROID PATIENTS

Pre-TSH (%)	Post-TSH (%)	Increment	Pre-TSH (%)	Post-TSH (%)	Increment	Pre-TSH (%)	Post-TSH (%)	Increment
11	36	(25)	7	26	(19)	20	64	(44)
3	55	(52)	10	62	(52)	3	41	(38)
21	33	(12)	2	30	(28)	20	48	(28)
7	46	(39)	5	57	(52)	17	36	(19)
7	35	(28)	3	30	(27)	9	24	(15)
8	35	(27)	2	86	(78)	16	34	(18)
			Mean 9.5	42.9	(33.4)			

subjects are shown in Tables 1 and 2 for the one- and three-dose stimulation tests, respectively. The means (+s.e.) for the Southern California subjects are compared with the corresponding means for the Alabama subjects reported by Taunton, et al (*1*) in Fig. 1. Not only the pre-TSH uptakes, but also the post-TSH uptakes and increments in uptake are significantly lower in the subjects with higher iodine intake when a single dose of TSH was used. However, after three doses of TSH the post-TSH uptakes and increments were not significantly different ($p > 0.05$) between the two groups despite an apparently larger increment in the higher iodine intake group.

It is not known what effect individual variation in the pre-TSH uptake has on the post-TSH uptake or increment in uptake. Hence these relationships were studied.

The effect of individual variation in the pre-TSH uptake on the post-TSH uptake as studied by regression analysis is shown in Fig. 2 for the one-dose stimulation test. After a single injection of TSH, the post-TSH uptake is a function of the pre-TSH uptake. The data from subjects with lower iodine intake (*1*) are similarly plotted and show the same within-group correlation. The slope of the regression line for the lower iodine intake group is not significantly different ($p > 0.05$) from the slope of the regression line for the higher iodine intake group and the slope of the regression line for the combined data is also plotted. None of the three regression lines has a slope significantly different from 1.00.

The effect of variation in the pre-TSH uptake on the increment in uptake is similarly plotted in Fig. 3 for the one-dose stimulation test. The slope of the regression line for the group of subjects with lower iodine intake (*1*) is not significantly different ($p > 0.05$) from the slope of the regression line for the group with the higher iodine intake, and the regression line for the combined data is also shown. None of the slopes is significantly different from zero.

The effect of individual variation in the pre-TSH uptake on the post-TSH uptake for the three-dose stimulation tests is shown in Fig. 4. After 3 days of TSH stimulation the post-TSH uptake is independent of the pre-TSH uptake in both groups. The slopes of the regression lines for the two groups of subjects are not significantly different ($p > 0.05$), and the

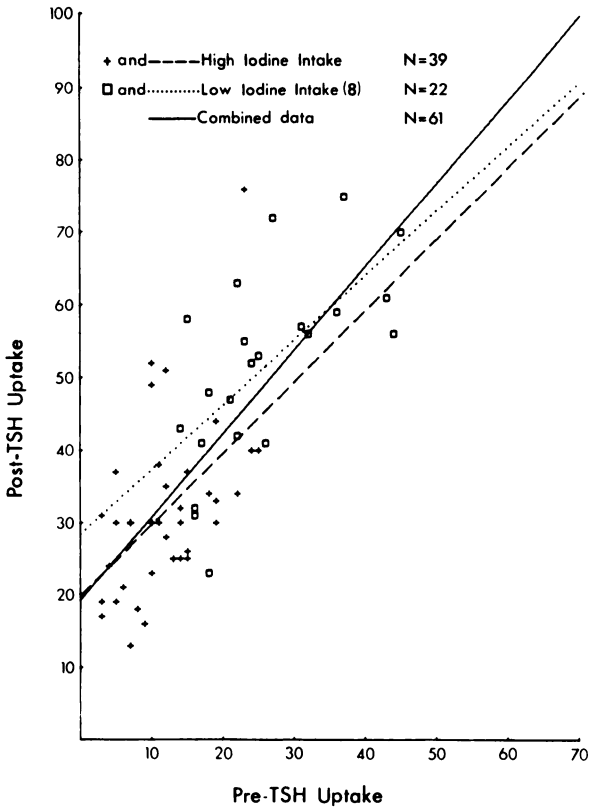

FIG. 2. Relationship of post-TSH RAI uptake after single injection of TSH to pre-TSH RAI uptake.

regression line for the combined data is also shown. The regression line for the combined data has a slope of —0.02 which is not significantly different from zero.

The effect of variation in the pre-TSH uptake on the increment in uptake after 3 days of TSH stimulation is shown in Fig. 5. The increment in uptake is inversely related to the pre-TSH uptake. The slope of the regression line for the lower iodine intake group is again not significantly different ($p > 0.05$) from that for the higher iodine intake group. The regression line for the combined data has a slope of —1.04 which is not significantly different from —1.

The mean increment in uptake was not greater following three doses of TSH (25.3) than following one dose of TSH (25.6) in the lower iodine intake group. By contrast, in the higher iodine intake group the mean increment following three doses of TSH (33.4) was significantly greater ($p < 0.001$) than following a single dose of TSH (19.7). The uptakes reached after the three-dose stimulation in the higher iodine intake group (mean 42.9%) were not significantly different ($p > 0.05$) from those reached by the lower iodine intake group after a single dose (mean 51.6%).

Hypothyroid patients. The results of TSH stimulation tests in 66 patients with primary hypothyroidism are shown in Table 3. Nineteen patients with primary hypothyroidism received a single dose of 5 units of TSH and had a mean increment in RAI uptake of -1.2 ± 0.6 ($\pm$sem) while 47 patients received three doses of 10 units of TSH and had a mean increment in RAI of 0.1 ± 0.4 ($\pm$sem). The responses to the two different stimulation tests are not significantly different ($p > 0.05$) so the two groups are combined. The range of increments in all 66 patients is from —7 to +10 with a mean of —0.3. There is no significant difference in the pre-TSH RAI uptakes, the post-TSH RAI uptakes, or the increments in uptake between these patients and the 15 primary hypothyroid Alabama patients reported by Taunton, et al (*1*) and in neither group was there a difference in response between the one- and three-dose tests (*1*).

The results in 19 patients with pituitary failure and a PBI or total thyroxine level below normal are shown in Table 4. The mean pre-TSH uptake is 7.0%, the mean post-TSH uptake is 34.4%, and the mean increment in uptake 27.4 after three doses of TSH. These are not significantly different ($p > 0.05$) from the means of 2%, 30%, and 28%

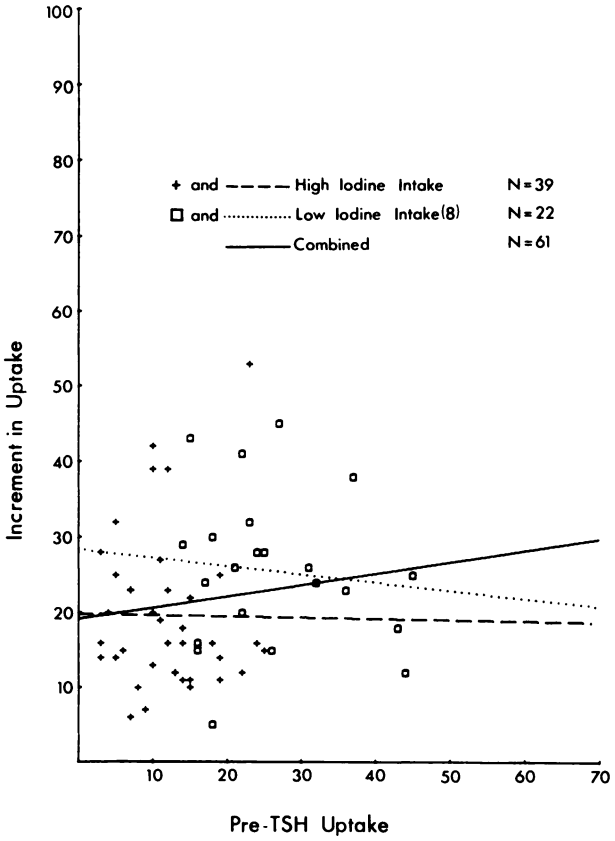

FIG. 3. Relationship of increment in RAI uptake after single injection of TSH to pre-TSH RAI uptake.

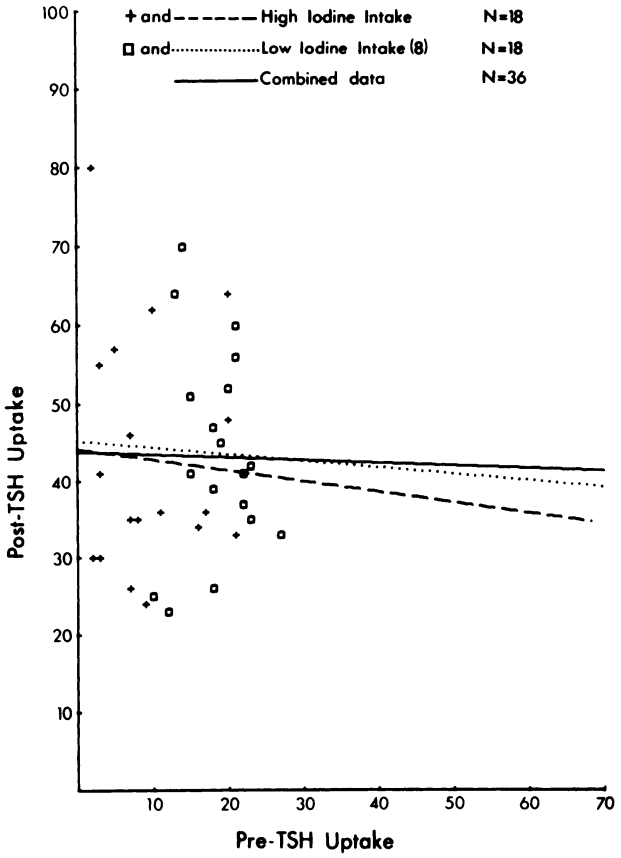

FIG. 4. Relationship of post-TSH RAI uptake after three injections of TSH to pre-TSH RAI uptake.

for five cases of hypopituitarism due to miscellaneous causes reported by Taunton, et al (*1*).

DISCUSSION

Dietary iodine intake varies with geographic location (*4,6,9*) and may change in a given location with changes in the preparation of foodstuffs (*10*). The level of plasma inorganic iodide (PII) is a direct function of dietary iodine intake (*13*). The renal clearance of iodide is constant in normal subjects over wide ranges in iodine intake and PII level (*14*); therefore urinary iodine excretion is also a direct function of dietary iodine intake (*13*). The RAI uptake is inversely related to the PII level (*15*) and the mean 24-hr RAI uptake of normal subjects is inversely related to the mean urinary iodide excretion (*16*). Therefore, as Oddie, et al (*4,9*) have shown, the mean iodine intakes of normal subjects can be calculated from mean 24-hr RAI uptakes. The high iodine intake group in this study had a calculated iodine intake 3½ times as great as the low iodine intake group.

Einhorn (*2*) has shown that the thyroidal accumulation of RAI is maximally stimulated by TSH doses of 0.025 USP units/kg. Since both the 5- and 10-unit doses are considerably in excess of this, the difference between the response to the one-dose stimulation test and the three-dose stimulation test is probably not due to the difference in the number of units given. Taunton, et al (*1*) also found no difference between the responses to 5 and 10 units of TSH. This suggests that the differing responses after three doses of TSH are due to the length of stimulation.

Following a single injection of TSH the increment in the individual 24-hr RAI uptake was independent of the level of the pre-TSH uptake over the range of pre-TSH uptakes studied (3–45%). Therefore the increment in uptake provides a suitable measure of response for comparing individuals with widely differing levels of iodine intake and pre-TSH uptakes. Since the increment in uptake is as great or greater following a three-dose stimulation test than following a one-dose stimulation test, there may be a level of increment that is useful for differentiating euthyroid responses from the responses in primary hypothyroidism. Fifty-five (96.5%) of the 57 euthyroid patients had increments of 10 or more while 65 (98.5%) of the 66 patients with primary hypothyroidism had an increment of less than 10. With a three-dose stimulation test 18 (94.7%) of

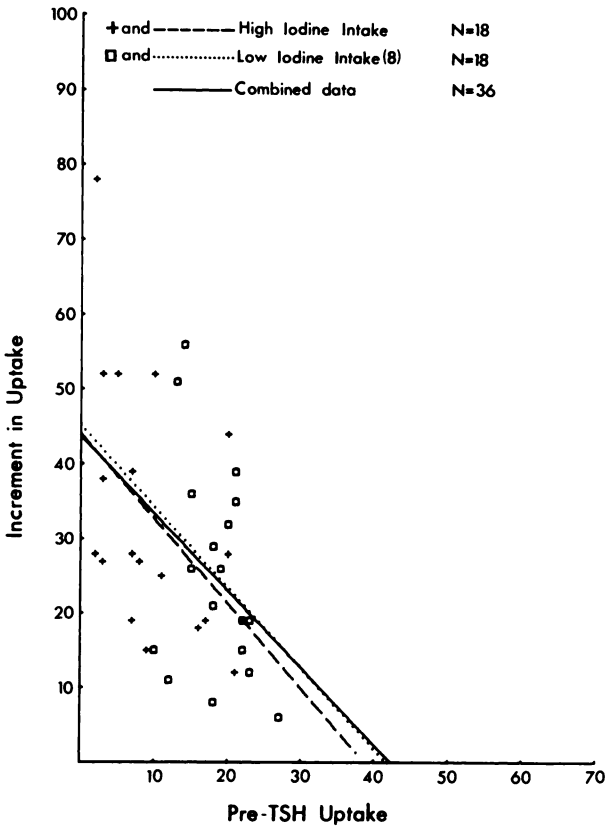

FIG. 5. Relationship of increment in RAI uptake after three injections of TSH to pre-TSH RAI uptake.

TABLE 3. 24-HR THYROIDAL UPTAKE BEFORE AND AFTER TSH IN 66 PATIENTS WITH PRIMARY HYPOTHYROIDISM

Pre-TSH (%)	Post-TSH (%)	Increment	Pre-TSH (%)	Post-TSH (%)	Increment	Pre-TSH (%)	Post-TSH (%)	Increment
4	2	(—2)	15	12	(—3)	20	18	(—2)
4	3	(—1)	1	1	(0)	9	11	(2)
4	2	(—2)	19	14	(—5)	13	15	(2)
3	3	(0)	10	7	(—3)	10	6	(—4)
1	2	(1)	2	3	(1)	1	3	(2)
15	15	(0)	2	5	(3)	22	18	(—4)
23	24	(—1)	6	8	(2)	11	4	(—7)
1	3	(2)	1	1	(0)	10	3	(—7)
8	8	(0)	4	5	(1)	8	6	(—2)
3	6	(3)	6	0	(—6)	3	3	(0)
10	12	(2)	1	6	(5)	1	1	(0)
2	5	(3)	1	2	(1)	3	3	(0)
1	1	(0)	10	9	(—1)	11	11	(0)
1	1	(0)	20	19	(—1)	3	3	(0)
1	2	(1)	1	1	(0)	2	2	(0)
3	4	(1)	1	1	(0)	6	8	(2)
2	1	(—1)	5	4	(—1)	11	11	(0)
2	1	(—1)	2	2	(0)	3	3	(0)
1	1	(0)	10	3	(—7)	2	3	(1)
1	2	(1)	3	1	(—2)	1	3	(2)
5	8	(3)	9	4	(—5)	2	2	(0)
3	13	(10)	6	4	(—2)	2	2	(0)
			Mean 5.9	5.6	(—0.3)			

TABLE 4. 24-HR THYROIDAL UPTAKE BEFORE AND AFTER THREE DOSES OF TSH IN 19 PATIENTS WITH PITUITARY HYPOTHYROIDISM

Pre-TSH (%)	Post-TSH (%)	Increment	Pre-TSH (%)	Post-TSH (%)	Increment	Pre-TSH (%)	Post-TSH (%)	Increment
9	39	(30)	1	54	(53)	5	50	(45)
12	30	(17)	14	30	(16)	13	65	(43)
15	44	(29)	5	18	(13)	1	22	(21)
9	48	(39)	8	40	(32)	2	23	(21)
2	20	(18)	2	9	(7)	16	41	(25)
2	25	(23)	1	24	(23)	2	23	(21)
13	49	(36)						
			Mean 7.0	34.4	(27.4)			

the patients with hypopituitarism had increments of 10 or more. Therefore an increment of 10 or more provides a useful definition of "normal" response. This confirms the findings of Bishopric, et al (*17*). In differentiating normal from primary hypothyroidism a one-dose test was satisfactory but to distinguish among patients with hypothyroidism, those with pituitary failure (TSH deficiency) required a three-dose test.

The only variables by which the two groups compared here are known to differ are the levels of iodine intake and RAI uptake. It can be concluded that the difference in response to a single dose of TSH is the result of the difference in iodine intake. This difference in increment disappears after three doses of TSH when the increment in the higher iodine intake group is no longer significantly different from that in the lower intake group and neither is different from that in the lower intake group following one dose of TSH indicating that increased iodine intake delays the full effect of TSH on thyroidal iodide accumulation.

Euthyroid subjects with higher dietary iodine intakes have higher absolute thyroidal iodide uptakes (AIU) (*13,15*). Since the increment in RAI uptake after three doses of TSH is not different between the two groups but iodine intakes, hence AIU, are different, the subjects with higher iodine intake (hence higher PII) would seem to have a proportionately similar but absolutely greater rise in AIU after TSH. This suggests that the magnitude of the increase in AIU after short-term TSH stimulation is a function of the level of AIU before stimulation.

There were no apparent differences in the RAI

uptakes or responses to TSH stimulation between the two groups of patients with primary or secondary hypothyroidism who had differing levels of iodine intake.

SUMMARY

The response of the thyroidal accumulation of iodide to TSH stimulation varies with the level of iodine intake. Increased iodine intake decreases both the pre- and the post-TSH RAI uptake when only one dose of TSH is given. The increment in RAI uptake after one dose of TSH is independent of the level of RAI uptake before stimulation but is decreased when iodine intake is increased. The effect of increased iodine intake disappears after three doses of TSH. An absolute increment in 24-hr RAI uptake of ten or more after TSH stimulation provides a useful dividing line for distinguishing euthyroid responses from the response in primary hypothyroidism in subjects with differing levels of iodine intake after either one or three doses of TSH.

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