NOTE

Comparison between the Thyrotropin Response to Thyrotropin-Releasing Hormone in Summer and That in Winter in Normal Subjects

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Synopsis

A comparison was made between the thyrotropin (TSH) response to 500 μ g thyrotropin-releasing hormone (TRH) in summer and that in winter in ten healthy normal adults living in Sapporo. The serum resin triiodothyronine (T_3) uptake (RT_3U), thyroxine (T_4) and T_3 levels were also measured. While the TSH response to TRH in summer was similar to that in winter, serum T_3 concentration and free T_3 index were significantly higher in winter than in summer, associated with the similar values in RT_3U and T_4 levels in serum. Independently measured 86 specimens (43 in summer and 43 in winter) from normal adults living in the same district also showed a significant increase in serum free T_3 index as well as a slight elevation of serum T_3 concentration in winter but not in serum T_4 level. These results indicate that the primary change in cold winter would be the stimulation of peripheral conversion of T_4 to T_3 rather than the activation of hypothalamo-pituitary-thyroid axis. The relevance of this interpretation was discussed.

It is generally accepted that thyroid hormone has an important role for non-shivering thermogenesis in cold acclimation (Smith and Hoijer, 1962; Hoch, 1974). Early studies in normal adults in various regions of the world have shown a seasonal variation of serum thyroid hormone concentrations (Oshiba *et al.*, 1957; Watanabe *et al.*, 1963; DuRuisseau, 1965; Nagata *et al.*, 1976; Smals *et al.*, 1977). The elevation of serum thyroid hormone concentration during winter has been interpreted in this way that it is because the pituitary-thyroid axis is activated by prolonged cold exposure, thereby secreting more thyroid hormone, but no data are available to prove the concomitant rise of serum thyroid-stimulating hormone (TSH) concentration during winter (Hedstrand and Wide, 1973; Rastogi

and Sawhney, 1976; Nagata *et al.*, 1976). In this communication, a study was undertaken to compare the TSH response to thyrotropin-releasing hormone (TRH) in summer with that in winter, in normal adults living in Sapporo, the northern part of Japan. The seasonal variation of serum thyroid hormone concentration was also investigated.

Materials and Methods

Ten healthy subjects (7 male and 3 female) living in Sapporo (43°03' N, 141°20' E), aged 21 to 64, participated in this study. None of them had either historical or physical findings of any endocrine-metabolic disorders. No special restrictions were made on their physical activity, food intake, clothing and climate conditioning. Blood specimens were obtained in the morning after overnight fast both in summer (July or August) and in winter (January or February) and sera obtained were stored at -20°C until used. Synthetic TRH (Tanabe Pharmaceutical Co.) 500 μ g

was given iv as a single bolus between 0900 and 1000 hr and blood sample for TSH was drawn at 0, 15, 30, 60 and 120 min. after injection. Measurements of serum triiodothyronine (T_3) and TSH by radioimmunoassay were made simultaneously for both summer and winter samples.

86 serum specimens from normal adults were also included as the laboratory control, in which 43 specimens (22 male, 21 female, mean age: 36) were obtained in July or August, 1976 and 43 specimens (23 male, 20 female, mean age: 34) in January or February 1977. Measurements of serum resin T_3 uptake (RT_3U), thyroxine (T_4) and T_3 of these specimens were taken on each occasion.

The mean ambient temperature obtained from the official weather station in Sapporo was -7.5°C – -5.5°C in winter and 20.3°C – 21.3°C in summer.

Serum T_4 and RT_3U were measured by Tetrasorb-kit and Triosorb-kit respectively (Abbott Laboratories). Serum TSH was measured by double antibody radioimmunoassay using the test kit (HTSH-kit, Daiichi RI Laboratories). Serum T_3 was measured by radioimmunoassay using the test kit (T_3 RIA kit, Dainabot RI Laboratories), in which bound and free antigen were separated by the dextran-coated charcoal method. The minimum detectable amount and precision of assay were described elsewhere (Konno, 1976). Free T_4 index and free T_3 index were calculated as previously described (Konno, 1974). The same control serum was always processed simultaneously and between-assay coefficients of variation in summer and in winter were as follows; T_4 : $7.7 \pm 0.5 \mu\text{g/dl}$ (6.5%) in summer and $7.6 \pm 0.5 \mu\text{g/dl}$ (6.6%) in winter, T_3 : $132 \pm 13 \text{ ng/dl}$ (9.6%) in summer and $122 \pm 10 \text{ ng/dl}$ (8.2%) in winter, RT_3U : $31.3 \pm 0.7\%$ (2.2%) in summer and $30.1 \pm 1.9\%$ (6.3%) in winter, TSH: $7.7 \pm 0.5 \mu\text{U/ml}$ (6.5%) in summer and $7.6 \pm 0.5 \mu\text{U/ml}$ (6.6%) in winter.

For statistical analysis, Student's *t* test was used and in 10 subjects paired analysis was attempted.

Results

Serum RT_3U , T_4 and free T_4 index values in 10 normal subjects were almost the same both in summer and in winter (Table 1). The values of the laboratory control, measured on the same occasion, also showed no seasonal changes in RT_3U , T_4 and free T_4 index in serum. Serum T_3 concentration in 10 subjects was significantly higher in winter than in summer: $195 \pm 34 \text{ ng/dl}$ (mean $\pm$ S.D.) *vs* $154 \pm 40 \text{ ng/dl}$ ($p < 0.001$). The elevation of serum T_3 concentration was seen in all subjects studied and the calculated free T_3 index was also significantly increased in winter compared with that in summer: 185 ± 24 *vs* 154 ± 22 ($p < 0.001$). The difference in serum T_3 concentration of the laboratory control was not statistically significant between two seasons, but the calculated normal range in summer and winter was 90–220 ng/dl and 100–230 ng/dl, respectively. Free T_3 index in summer was 155 ± 28 and 168 ± 29 in winter, the difference between the two values being statistically significant ($p < 0.05$).

TSH response to 500 μg TRH was examined in 10 normal adults and the similar pattern of response was observed between two seasons (Fig. 1). Basal TSH concentration was $2.2 \pm 0.4 \mu\text{U/ml}$ in summer and $1.9 \pm 0.4 \mu\text{U/ml}$ in winter and the peak value of TSH after TRH in summer and

Table 1. Comparison of serum resin triiodothyronine (T_3) uptake (RT_3U), thyroxine (T_4), T_3 , free T_4 index and free T_3 index between in summer and in winter in 10 normal subjects and 86 laboratory control specimens.

subjects	season	RT_3U (%)	T_4 ($\mu\text{g/dl}$)	T_3 (ng/dl)	free T_4 index	free T_3 index
10	summer	31.0 ± 4.5	9.0 ± 1.0	154 ± 40	9.3 ± 1.9	154 ± 22
	winter	29.4 ± 4.3	9.5 ± 1.8	195 ± 34	9.3 ± 2.2	185 ± 24
p**		ns	ns	$p < 0.001$	ns	$p < 0.001$
Laboratory control						
43	summer	30.2 ± 2.7	9.4 ± 1.5	153 ± 32	9.5 ± 1.4	155 ± 28
43	winter	30.1 ± 3.0	9.2 ± 1.4	168 ± 36	9.2 ± 1.3	168 ± 30
p		ns	ns	$0.05 < p < 0.1$	ns	$p < 0.05$

* mean $\pm$ S.D.

** analysis by paired *t* test

Fig. 1. Serum TSH response to TRH in normal subjects in summer and in winter. TRH-test in 10 normal subjects was performed in summer (July or August, 1976) and in winter (January or February, 1977). Values are expressed as mean $\pm$ SEM. Shaded area encompasses the normal range of response.

in winter was $15.2 \pm 3.1 \mu\text{U/ml}$ and $14.1 \pm 2.8 \mu\text{U/ml}$, respectively. Mean maximal TSH increments after TRH (ΔTSH) were $13.0 \mu\text{U/ml}$ in summer and $12.7 \mu\text{U/ml}$ in winter. The difference of ΔTSH between two seasons was $4.1 \pm 3.1 \mu\text{U/ml}$ (range, 0.1–8.5 $\mu\text{U/ml}$).

Discussion

The present study demonstrated that normal adults living in Sapporo showed a serum T_3 concentration significantly higher in winter than in summer, whereas TSH responsiveness to TRH as well as serum T_4 concentration was similar between two seasons. Simultaneous measurement of RT_3U failed to show any seasonal changes, indicating that serum free- T_3 concentration was also elevated during winter as reflected by the increase in free- T_3 index (Konno, 1974).

Although several investigators reported a winter-related elevation of serum thyroid hormone concentration, there is a disagree-

ment whether this occurred in either serum T_4 or T_3 or in both T_4 and T_3 : elevation of PBI (Oshiba *et al.*, 1957; Watanabe *et al.*, 1963; DuRuisseau, 1965), elevation of both T_4 and T_3 (Smals *et al.*, 1977) or of T_3 only (Nagata *et al.*, 1976). The reasons for these differences are uncertain. The present results are in agreement with the data of Nagata *et al.* were obtained in normal subjects in Kajimadaira where the ambient temperatures in summer and in winter are comparable to those in Sapporo, although the climate conditioning is markedly different. It was also confirmatory that the independently obtained values of the laboratory control in our hands showed a slightly higher normal range of serum T_3 concentration and a significantly elevated free- T_3 index in winter.

It is well known that the acute cold exposure of experimental animals evoked a brief elevation of serum TSH concentration (Bottari, 1957; Itoh *et al.*, 1966; Konno and Koseki, 1967; Yamada *et al.*, 1965; Hefco *et al.*, 1975; Tal *et al.*, 1976). Even in prolonged exposure to cold, TSH elevation was transient, followed by a return toward the basal level (Itoh *et al.*, 1966; Hefco *et al.*, 1975). Most studies in human adults, on the contrary, failed to find not only the brief elevation of the serum TSH level by acute body cooling (Odell *et al.*, 1967; Golstein-Golair *et al.*, 1970; Hershtman *et al.*, 1970; Fisher *et al.*, 1971) but also any seasonal changes in serum TSH concentration despite the elevated serum or urinary thyroid hormone concentrations (Hedstrand and Wide, 1973; Rastogi and Sawhney, 1976; Nagata *et al.*, 1976). Although only one dose of TRH (500 μg) was tested in the present study, the similar TSH response to TRH both in summer and in winter also indicated that the TSH secretory responsiveness of the pituitary to TRH remained unchanged in winter despite the elevated serum T_3 concentration.

Since a small amount of TSH produces

an increase of serum T_3 concentration but not T_4 (Snyder and Utiger, 1973; Rabello *et al.*, 1974), it would be possible that the elevation of T_3 in winter might be produced by the minor and gradual increase in serum TSH which was unassessable by the present radioimmunoassay method.

It has been shown that only minimum changes in serum thyroid hormone concentration, still within the normal range, sensitively affect the TSH response to TRH (Snyder and Utiger, 1972; Vagenakis *et al.*, 1974). Hefco *et al.*, in their studies on the effect of acute exposure of rats to cold, suggested that *in vivo* pituitary responsiveness to TRH was determined by the serum thyroid hormone concentration rather than the pituitary TSH content (Hefco *et al.*, 1975). Chopra *et al.* proposed that serum T_4 but not T_3 would be the determinant of TSH secretion (Chopra *et al.*, 1973). This proposal was supported by Sawin *et al.*, who showed a significant inverse relation between peak TSH after TRH and serum T_4 but not T_3 in normal subjects (Sawin and Hershman, 1976). In view of these findings, the similarity between TSH response to TRH in summer and that in winter, in the present study, may be expected from the similarity between the serum T_4 concentration in two seasons. Therefore, it is probable that the elevation of serum T_3 concentration in winter would neither result in an inhibition of TSH response to TRH nor result from the preferential secretion of T_3 from the thyroid.

The possible cause of increased serum T_3 concentration in winter would be the stimulation of peripheral conversion from T_4 . Bernal *et al.* reported that the acclimation to cold environment of thyroidectomized rats maintained on a constant dose of T_4 induced the increased conversion of T_4 to T_3 (Bernal *et al.*, 1975). A similar study is in progress in our laboratory with the primary hypothyroid patients receiving a constant dose of T_4 . Preliminary

results show an elevation of serum T_3 concentration during winter associated with significant decrease in serum free- T_4 index level (unpublished observation). These results may be compatible with the idea that the activation of peripheral conversion of T_4 to T_3 occurs primarily in winter. This process, if in operation, is to compensate the cold by increasing the basal metabolic rate.

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References

- Bernal, J. and F. Escobar del Rey (1975). *Acta Endocrinol. (Kbh.)* 78, 481.
- Bottari, P. M. (1957). *Ciba Found. Colloq. Endocrinol.* 11, 52.
- Chopra, I. J., D. H. Solomon and G. N. C. Teco (1973). *J. Clin. Endocrinol. Metab.* 36, 1050.
- DuRuisseau, J. P. (1965). *ibid.* 25, 1513.
- Fisher, D. A. and W. D. Odell (1971). *ibid.* 33, 859.
- Golstein-Golatre, J., L. Vanhaelst, O. D. Bruno, R. Leclercq and G. Copinschi (1970). *J. Appl. Physiol.* 29, 622.
- Hedstrand, H. and L. Wide (1973). *Brit. Med. J.* 17, 420.
- Hefco, E., L. Krulich, P. Illner and P. R. Larsen (1975). *Endocrinology* 97, 1185.
- Hershman, J. M., D. G. Read, A. L. Bailey, V. P. Norman and T. B. Gibson (1970). *J. Clin. Endocrinol. Metab.* 30, 430.
- Hock, F. L. Handbook of Physiol. (edited by M. A. Greer and D. H. Solomon) Section 7, Endocrinol. Vol. III, Thyroid p. 391. (1974).
- Itoh, S., T. Hiroshige, T. Koseki and Nakatsugawa (1966). *Fed. Proc.* 25, 1187.
- Konno, N. and T. Koseki (1967). *Folia Endocrinol. Jap.* 42, 1227. (In Japanese).
- Konno, N. (1974). *ibid.* 50, 711. (In Japanese).
- Konno, N. (1976). *Endocrinol. Japon.* 23, 313.
- Nagata, H., T. Izumiyama, K. Kawata, S. Kono, Y. Yukimura, M. Towata, T. Aizawa and T. Yamada (1976). *J. Clin. Endocrinol. Metab.* 43, 1153.

- Odell, W. D., J. F. Wilber and R. D. Utiger (1967). *Recent Prog. Hormone Res.* 23, 47.
- Oshiba, S. (1957). *Jap. J. Physiol.* 7, 335.
- Rabello, M. M., P. J. Snyder and R. D. Utiger (1974). *J. Clin. Endocrinol. Metab.* 39, 571.
- Rastogi, G. K. and R. C. Sawhney (1976). *Metabolism* 25, 903.
- Sawin, G. T. and J. M. Hershman (1976). *J. Clin. Endocrinol. Metab.* 42, 809.
- Smals, A. G. H., H. A. Ross and P. W. C. Kloppenborg (1977). *ibid.* 44, 998.
- Smith, R. E. and D. J. Hoijer (1962). *Physiol. Rev.* 42, 60.
- Snyder, P. J. and R. D. Utiger (1972). *J. Clin. Invest.* 51, 2077.
- Snyder P. J. and R. D. Utiger (1973). *ibid.* 52, 2305.
- Tal, E., R. Chayoth, U. Zor, G. Goldhaber and A. Zerachie (1976). *Acta Endocrinol. (Kbh.)* 83, 99.
- Vagenakis, A., B. Rapoport, F. Azizi, G. I. Portnay, L. E. Braverman and S. H. Ingbar (1974). *J. Clin. Invest.* 54, 913.
- Watanabe, G., M. Uematsu and K. Morii (1963). *J. Clin. Endocrinol. Metab.* 23, 383.
- Yamada, T., A. Kajihara, T. Onaya, I. Kobayashi, Y. Takemura and K. Shichijo (1965). *Endocrinology* 77, 968.