Total and free thyroid hormone concentrations after elective surgery

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SUMMARY Changes in thyroid hormone concentration and distribution and plasma cortisol levels have been followed in 11 patients undergoing elective cholecystectomy. A significant rise in total and free thyroxine (T4) and fall in total and free triiodothyronine (T3) were noted after surgery. Reverse T3 concentrations rose substantially, suggesting that peripheral conversion of T4 to T3 is diminished and that there is preferential formation of reverse T3. Serum thyroid stimulating hormone concentrations did not change. There was no direct correlation between the change in cortisol and the change in thyroid hormone or reverse T3 concentrations.

Marked changes in circulating triiodothyronine (T3) and reverse triiodothyronine (rT3) have been reported in association with acute and chronic illness and after surgery (Carter *et al.*, 1974; Bermudez *et al.*, 1975; Burr *et al.*, 1975; Chopra *et al.*, 1975a; Brandt *et al.*, 1976a; Brandt *et al.*, 1976b; Burger *et al.*, 1976). There is evidence that these changes result from reduced clearance and possibly an increased peripheral production of rT3 and a reduction in T3 derived from T4 by the peripheral tissues (Burr *et al.*, 1975; Chopra, 1976). It had been suggested that these changes are a result of increased cortisol secretion since similar changes are seen after the administration of large doses of dexamethasone (Duick *et al.*, 1974; Chopra *et al.*, 1975b; Burr *et al.*, 1976) but this hypothesis has been challenged by a recent study (Brandt *et al.*, 1976b). It has also been demonstrated that there is reduced binding of thyroid hormones by the transport proteins after surgery (Brandt *et al.*, 1976b), and earlier studies suggest that this results from a fall in thyroxine-binding prealbumin capacity (Kirby *et al.*, 1973).

The objective of this study was to confirm the change in thyroid hormone concentration after surgery in relation to plasma cortisol levels and to examine the distribution of thyroid hormone

between the bound and free fractions in the serum by direct radioimmunoassay techniques.

Patients and methods

During admission for elective cholecystectomy 11 women (age 27-67) were studied. None had any other detectable illness and all were clinically and biochemically euthyroid. All had a peroperative cholangiogram carried out using Hypaque^(R) 25%, and it has been shown previously that this compound is excreted rapidly unchanged (McChesney and Hoppe, 1957). The observations of Bürgi *et al.* (1976) also suggest that alterations of thyroid function will only occur after oral cholecystography. A record of anaesthetic agents, premedication, and drugs used in the postoperative period was kept on each patient. None of the subjects required a blood transfusion.

A venous blood sample was obtained from each patient the day before operation (day 1), the day of operation (day 2), and daily thereafter. Each sample was assayed for total T4 and T3 (Evered *et al.*, 1976), free T4 and T3 (Yeo *et al.*, 1977), rT3 (Ratcliffe *et al.*, 1976), and thyroid stimulating hormone (TSH) (Hall *et al.*, 1971) using specific radioimmunoassays. A thyroid hormone binding test (Thyopac-3^(R), Radiochemical Centre, Amersham) and plasma cortisol estimation (Mattingly, 1962) were also carried out in each sample. Each sample was obtained at the same time each day (1700 hours).

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Results

TOTAL THYROID HORMONE CONCENTRATIONS

Total T4 values rose after surgery by 11% compared with the preoperative day. The peak value was reached on day 4, and the value was significantly elevated on days 4-6. Total T3 values fell progressively by 33%, reaching their nadir on day 5 and were

Figure Total and free T4 and T3 levels and reverse T3 after elective surgery.

significantly depressed compared with day 1 from days 2 to 7. These changes are shown in the Figure and Table.

FREE THYROID HORMONE CONCENTRATIONS

Free T4 values rose progressively after surgery by 37% and the peak value was reached on day 4. The values were significantly elevated compared with day 1 from days 2 to 5. Free T3 values fell progressively by 51% after surgery. The nadir was reached on day 7, but marked and significantly reduced levels were noted on all the postoperative days (Figure and Table).

rT3 CONCENTRATIONS

rT3 concentrations rose by 137% after surgery to a peak on day 4. The level was significantly raised from days 2 to 7.

TSH CONCENTRATIONS

Serum TSH concentration did not change during the course of the study, the mean values for each day falling between 1.4 and 2.9 mU/l; 17% of observations fell below the lower limit of detection of the assay.

THYROID HORMONE BINDING TEST (THYOPAC-3^(R))

The Thyopac-3 value fell by 9% on day 3, reflecting a reduction in residual binding capacity. The Thyopac-3 value was significantly depressed from days 2 to 6 (Figure and Table).

PLASMA CORTISOL (11-HYDROXYCORTICOSTEROID CONCENTRATION)

Plasma cortisol concentrations rose promptly after surgery, being at their highest level on the day of operation, and declined progressively thereafter (Table). There was no direct correlation between the

Table Total and free thyroid hormone concentrations, rT3, Thyopac-3^(R), and cortisol after surgery

Day	TT4 (nmol/l)	FT4 (pmol/l)	TT3 (nmol/l)	FT3 (pmol/l)	rT3 (nmol/l)	Thyopac-3	Cortisol (mmol/l)
1	104 ± 5	8.4 ± 0.5	1.70 ± 0.10	10.5 ± 0.8	0.26 ± 0.02	117 ± 3	502 ± 44
2	110 ± 7	10.3 ± 0.7*	1.27 ± 0.10*	7.1 ± 1.3*	0.44 ± 0.06*	111 ± 3†	1751 ± 162*
3	112 ± 5	10.9 ± 0.7*	1.22 ± 0.13*	6.9 ± 1.3*	0.60 ± 0.07*	107 ± 2†	1101 ± 187†
4	115 ± 4*	11.2 ± 0.4*	1.15 ± 0.08*	6.0 ± 1.0*	0.63 ± 0.08*	109 ± 2†	944 ± 119†
5	111 ± 4*	9.9 ± 0.6*	1.14 ± 0.08*	6.2 ± 1.1*	0.51 ± 0.07*	112 ± 3*	745 ± 86†
6	110 ± 4*	9.8 ± 0.8	1.23 ± 0.08*	6.1 ± 1.0*	0.37 ± 0.05*	112 ± 2*	687 ± 51†
7	105 ± 4	8.8 ± 0.4	1.22 ± 0.13*	5.2 ± 1.0*	0.34 ± 0.05*	112 ± 2	645 ± 44†
8	102 ± 3	8.5 ± 0.7	1.31 ± 0.15	7.1 ± 1.1*	0.29 ± 0.03	115 ± 2	779 ± 74†

TT4 = total thyroxine, FT4 = free thyroxine, TT3 = total triiodothyronine, FT3 = free triiodothyronine, rT3 = reverse triiodothyronine

All values ± 1 SEM

*P < 0.05

†P < 0.01

‡P < 0.001

} Compared with day 1 using a paired *t* test

change in cortisol and the change in thyroid hormone or rT3 concentrations.

Discussion

The marked changes in T3 and rT3 concentrations in association with acute and chronic illness and malnutrition and after surgery have been reported by a number of authors (Carter *et al.*, 1974; Bermudez *et al.*, 1975; Burr *et al.*, 1975; Chopra *et al.*, 1975a; Brandt *et al.*, 1976a, b; Burger *et al.*, 1976). These data confirm the findings of other authors with respect to the total hormone concentrations. Recent work (Carter *et al.*, 1976) suggests that the peripheral conversion of T4 to T3 is diminished and that increased amounts of the alternative metabolite (rT3) are formed preferentially. There is growing evidence that more than one enzyme is involved and that there are specific deiodinases for inner and outer ring deiodination. The mechanism by which the peripheral production of T3 is diverted to rT3 remains uncertain. It had been suggested that these changes resulted from an increase in cortisol secretion since similar changes are seen after the administration of large doses of dexamethasone (Duick *et al.*, 1974; Chopra *et al.*, 1975b; Burr *et al.*, 1976). This view was, however, questioned by Brandt *et al.* (1976b), who showed that these changes in thyroid hormone concentrations occurred in patients undergoing abdominal surgery in whom afferent neurogenic impulses were blocked during and after operation by epidural analgesia—and in whom the stress-induced increase in cortisol was abolished. The absence of any temporal correlation between the changes in cortisol and thyroid hormone concentrations also indicates that these latter changes are not dependent upon a stress-induced increase in cortisol secretion. A number of the metabolic responses to surgical trauma are abolished by blocking afferent neurogenic stimuli from the operative field (including the changes in cortisol, glucose, cyclic-AMP, and growth hormone). Other responses, notably catecholamine release, however, are not abolished, and further study is required to identify the mechanisms involved. The physiological advantages and/or disadvantages of these adaptive changes remain obscure.

The rise in T4 conflicts with earlier reports of a small fall in T4 (Burr *et al.*, 1975) and unchanged PBI concentrations (Kirby *et al.*, 1973) but is consistent with the use in T4 reported by Brandt *et al.* (1976a, b) and the increase in T4 production rate reported by Harland *et al.* (1972). Similar rises in T4 after surgery under halothane anaesthesia have also been reported by Oyama and his colleagues (1969; 1972). The physiological significance of

these changes remains uncertain.

Free T4 and T3 levels showed qualitatively similar changes after surgery when compared with total T4 and T3. It was noted, however, that the amplitude of the free hormone changes was proportionately much greater than those of the total hormones. These changes indicate that the distribution of these hormones is altered by surgical stress, and it might be expected that they would be accompanied by an increased clearance of T4 from the circulation and a reduced clearance of T3. Changes consistent with this view have been reported postoperatively by Harland *et al.* (1972) for T4 and in sick euthyroid patients by Carter *et al.* (1976) for T3. The increase in T4 can be largely attributed to a progressive discharge of T4 from the liver (Harland *et al.*, 1974).

Current techniques are inadequate to establish all the factors that contribute to the changes in thyroid hormone concentrations, but changes in T4 and T3 production rate, alterations in thyroid hormone binding protein capacity, and alterations in cellular uptake, metabolism, and degradation have all been implicated by various authors. The metabolic factors that initiate these changes and the mechanisms by which they occur remain unclear.

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References

- Bermudez, F., Surks, M. I., and Oppenheimer, J. H. (1975). High incidence of decreased serum triiodothyronine concentration in patients with non-thyroidal disease. *Journal of Clinical Endocrinology and Metabolism*, **41**, 27-40.
- Brandt, M., Kehlet, H., Hansen, J. M., and Skovsted, L. (1976a). Serum triiodothyronine and surgery (Letter). *Lancet*, **1**, 491.
- Brandt, M. R., Kehlet, H., Skovsted, L., and Hansen, J. M. (1976b). Rapid decrease in plasma-triiodothyronine during surgery and epidural analgesia independent of afferent neurogenic stimuli and of cortisol. *Lancet*, **2**, 1333-1336.
- Burger, A., Nicod, P., Suter, P., Vallotton, M. B., Vagenakis, A., and Braverman, L. (1976). Reduced active thyroid hormone levels in acute illness. *Lancet*, **1**, 653-655.
- Bürki, H., Wimpfheimer, C., Burger, A., Zaunbauer, W., Rösler, H., and Lemarchand-Béraud, T. (1976). Changes of circulating thyroxine, triiodothyronine

- and reverse triiodothyronine after radiographic contrast agents. *Journal of Clinical Endocrinology and Metabolism*, **43**, 1203-1210.
- Burr, W. A., Griffiths, R. S., Black, E. G., Hoffenberg, R., Meinhold, H., and Wenzel, K. W. (1975). Serum triiodothyronine and reverse triiodothyronine concentrations after surgical operation. *Lancet*, **2**, 1277-1279.
- Burr, W. A., Ramsden, D. B., Griffiths, R. S., Black, E. G., Hoffenberg, R., Meinhold, H., and Wenzel, K. W. (1976). Effect of a single dose of dexamethasone on serum concentrations of thyroid hormones. *Lancet*, **2**, 58-61.
- Carter, J. N., Eastman, C. J., Corcoran, J. M., and Lazarus, L. (1974). Effect of severe, chronic illness on thyroid function. *Lancet*, **2**, 971-974.
- Carter, J. N., Eastman, C. J., Corcoran, J. M., and Lazarus, L. (1976). Inhibition of conversion of thyroxine to triiodothyronine in patients with severe chronic illness. *Clinical Endocrinology*, **5**, 587-594.
- Chopra, I. J. (1976). An assessment of daily production and significance of thyroïdal secretion of 3, 3', 5'-triiodothyronine (reverse T₃) in man. *Journal of Clinical Investigation*, **58**, 32-40.
- Chopra, I. J., Chopra, U., Smith, S. R., Reza, M., and Solomon, D. H. (1975a). Reciprocal changes in serum concentrations of 3, 3', 5'-triiodothyronine (reverse T₃) and 3, 3', 5'-triiodothyronine (T₃) in systemic illnesses. *Journal of Clinical Endocrinology and Metabolism*, **41**, 1043-1049.
- Chopra, I. J., Williams, D. E., Orgiazzi, J., and Solomon, D. H. (1975b). Opposite effects of dexamethasone on serum concentrations of 3, 3', 5'-triiodothyronine (reverse T₃) and 3, 3', 5'-triiodothyronine (T₃). *Journal of Clinical Endocrinology and Metabolism*, **41**, 911-920.
- Duick, D. S., Warren, D. W., Nicoloff, J. T., Otis, C. L., and Croxson, M. S. (1974). Effect of single dose dexamethasone on the concentration of serum triiodothyronine in man. *Journal of Clinical Endocrinology and Metabolism*, **39**, 1151-1154.
- Evered, D. C., Vice, P. A., Green, E., and Appleton, D. (1976). Assessment of thyroid hormone assays. *Journal of Clinical Pathology*, **29**, 1054-1059.
- Hall, R., Amos, J., and Ormston, B. J. (1971). Radioimmunoassay of human serum thyrotrophin. *British Medical Journal*, **1**, 582-585.
- Harland, W. A., Horton, P. W., Strang, R., Fitzgerald, B., Richards, J. R., and Holloway, K. B. (1974). Release of thyroxine from the liver during anaesthesia and surgery. *British Journal of Anaesthesia*, **46**, 818-820.
- Harland, W. A., Orr, J. S., and Richards, J. R. (1972). Increased thyroxine secretion following surgical operation. *Scottish Medical Journal*, **17**, 92-97.
- Kirby, R., Clark, F., and Johnston, I. D. A. (1973). The effect of surgical operation of moderate severity on thyroid function. *Clinical Endocrinology*, **2**, 89-99.
- McChesney, E. W., and Hoppe, J. O. (1957). Studies of the tissue distribution and excretion of sodium diazoate in laboratory animals. *American Journal of Roentgenology*, **78**, 137-144.
- Mattingly, D. (1962). A simple fluorimetric method for the estimation of free 11-hydroxycorticoids in human plasma. *Journal of Clinical Pathology*, **15**, 374-379.
- Oyama, T., Matsuki, A., and Kudo, T. (1972). Effect of halothane, methoxyflurane anaesthesia and surgery on plasma thyroid-stimulating hormone (TSH) levels in man. *Anaesthesia*, **27**, 2-8.
- Oyama, T., Shibata, S., Matsuki, A., and Kudo, T. (1969). Serum endogenous thyroxine levels in man during anaesthesia and surgery. *British Journal of Anaesthesia*, **41**, 103-108.
- Ratcliffe, W. A., Marshall, J., and Ratcliffe, J. G. (1976). The radioimmunoassay of 3, 3', 5'-triiodothyronine (reverse T₃) in unextracted human serum. *Clinical Endocrinology*, **5**, 631-641.
- Yeo, P. P. B., Lewis, M., and Evered, D. C. (1977). Radioimmunoassay of free thyroid hormone concentrations in the investigation of thyroid disease. *Clinical Endocrinology*, **6**, 159-165.

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