0021-972X/98/$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 83, No. 9
Printed in U.S.A.

Salsalate Administration—A Potential Pharmacological Model of the Sick Euthyroid Syndrome

RONG WANG, JERALD C. NELSON, AND R. BRUCE WILCOX

Departments of Biochemistry (R.W.) and Medicine (J.C.N.), School of Medicine, Loma Linda University, Loma Linda, California 92354; and Quest Diagnostics Nichols Institute (R.B.W.), San Juan Capistrano, California 92690

ABSTRACT

This study examined salsalate ingestion as a model of the sequelae of acute inhibition of thyroid hormone binding to serum protein. One dose of salsalate (60–65 mg/kg) was administered to healthy volunteers. Serum salsalate concentrations peaked at 2 h (82 μg/mL), then declined at 8 h to 1.2 μg/mL. Serum total T_4 (TT_4) and total T_3 (TT_3) concentrations declined for 4 h, then recovered by 96 h, while T_4 binding protein concentrations remained unchanged. TT_3 was reduced to a greater extent than TT_4 between 2 h and 72 h, and serum total reverse(r)T_3 (TrT_3) was transiently increased at 8 h. TSH concentrations fell while TT_4 and TT_3 fell, then recovered while TT_4, TT_3, and free T_3, but not free T_4, were still reduced. Subsequently, TSH overshot basal levels and continued to rise after 96 h while TT_4, TT_3, free T_4, free T_3, and TrT_3 were all at basal levels. We postulate that an acute release of T_4 and T_3 from circulating transport proteins, induced by an inhibitor of binding, can result in large and rapid redistribution of T_4 and T_3 into tissue compartments associated with transiently reduced peripheral tissue 5′-monodeiodination and deranged TSH regulation. (*J Clin Endocrinol Metab* **83:** 3095–3099, 1998)

THE FIRST step in thyroid hormone action is hormone transport from the thyroid gland through the circulation to target tissues. In normal serum, over 99.95% of T_4 and 99.5% of T_3 are bound to serum transport proteins (1). There are situations in which this binding is transiently decreased, including acute nonthyroidal illness and after administration of certain drugs (2–7). The consequences of acutely decreased binding are not yet fully elucidated.

Salsalate (Disalcid), a commonly used nonsteroidal antiinflammatory drug, is a known inhibitor of T_4 and T_3 binding to serum transport proteins (7). In humans, salsalate is absorbed completely through the gastrointestinal tract and then partially hydrolyzed to form salicylate, also an inhibitor of T_4 and T_3 binding to transport proteins (7, 8). Salsalate has been reported to reach peak serum levels approximately 1.5 h after a single oral dose, then disappear with a half-life of approximately 1 h (9, 10). Doses of salsalate that reduce serum total T_4 (TT_4) and total T_3 (TT_3) concentrations cause minor, if any, side effects. Consequently, salsalate administration should provide an acceptable agent for inducing short-term inhibition in thyroid hormone binding to transport proteins in experimental studies. Chronic administration of salsalate is reported to lead to reductions in serum TT_4 and TT_3 and to transient reduction in TSH (11–14). However, the acute thyroid and pituitary hormone changes after a single dose of salsalate have not been reported.

Our hypothesis is that acute inhibition of thyroid hormone binding to transport proteins by salsalate will be followed by a redistribution of thyroid hormones from the circulation into target tissues. The objective of this study was to investigate the thyroid hormone changes in healthy individuals after short-term perturbation by salsalate of thyroid hormone transport by serum proteins and their relationship to serum salsalate concentrations.

Received September 18, 1997. Revision received April 20, 1998. Rerevision received June 2, 1998. Accepted June 10, 1998.

Address all correspondence and requests for reprints to: R. Bruce Wilcox, Ph.D., Department of Biochemistry, Mortensen Hall, Room 209, Loma Linda University, Loma Linda, California 92354.

Materials and Methods

Study protocol

The study protocol was approved by the Loma Linda University Institutional Review Board. Five healthy, lean, nonpregnant, unmedicated adults (3 women and 2 men; age, 23–25 yr), selected for normal serum TSH, free T_4 (FT_4) and T_4-binding globulin (TBG) concentrations, volunteered for this study. Blood samples were obtained on days −7, 0, 1, 2, 3, 4, and 6 of the study. Blood samples were taken at 0800 h by venipuncture on each scheduled day, after an overnight fast. Basal samples were obtained on days −7 and 0, and zero-time values were the means of the two basal samples. Salsalate was administered at 0800 h on day 0 immediately after the second basal sample. On this day (day 0), fasting was extended to 1200 h, and additional blood samples were taken at 2 h, 4 h, and 8 h after salsalate ingestion. Days 1–6 were washout days. Each person took salsalate orally, 60–65 mg/kg BW [in our pilot study, the subject with the smallest BW (48 kg) took the recommended dosage of salsalate (3 g), which was calculated to be 62.5 mg/kg BW; to standardize the dosage of salsalate in our study for body weight, we use 60–65 mg/kg]. The individual dosages ranged between 3.4 g and 5.3 g and were above the usual recommended daily dosage of 3.0 g (which is given independent of body weight). Salsalate (Disalcid) was obtained from Goldline Laboratories, Ft. Lauderdale, FL (product no. 16790; lot no. L26801; 750 mg/tablet). Side effects were mild and transient and typical of high-dose salicylate administration. The most common were mild nausea and tinnitus. Sera were separated within 2 h after phlebotomy and frozen at −20 C until analysis. Sera were assayed for TT_4, TT_3, FT_4, free T_3 (FT_3), total reverse(r)T_3 (TrT_3), TSH, TBG, transthyretin (prealbumin), albumin, salsalate, and salicylic acid concentrations.

Analytical methods

Sera were assayed for TT_4 and TT_3 by RIA (normal ranges: TT_4, 5.3–10.5 μg/dL; TT_3, 70–204 ng/dL), for FT_4 by direct equilibrium dialysis (normal range, 0.8–2.7 ng/dL), for FT_3 by equilibrium tracer dialysis (normal range, 260–480 pg/dL), for TrT_3 by double-antibody RIA (normal range, 15–40 ng/dL), for TSH by third-generation immunochemiluminometric assay (normal range, 0.4–4.2 mU/L, calibrated to the World Health Organization TSH reference standard 80/558), for

thyroid hormone binding proteins by immunoassay methods (normal ranges: TBG, 1.2–3.0 mg/dL; transthyretin, 14–42 mg/dL; albumin, 3200–5500 mg/dL). Except for TrT_3, assays were performed at Quest Diagnostics Nichols Institute. TrT_3 was measured at the University of Southern California Endocrine Services Laboratory, Los Angeles, CA, using a specific rT_3 antiserum provided by Dr. T. J. Visser (15).

Salsalate and salicylic acid concentrations were measured by the high-performance liquid chromatography method described by Harrison *et al.* (10). Sera were separated as quickly as possible, then to 0.5-mL aliquots of serum were added 0.9 mL of 0.27 mol/L HCl, 10 μg of α-phenylcinnamic acid as an internal standard (100 μL of a 0.1 mg/mL solution in methanol; Aldrich Chemical Company, Inc., Milwaukee, WI, Catalog No. P2,200–1; Lot No. 03627JN), and 10 mL methylene chloride. The tubes were shaken for 15 min on a mechanical shaker at 125 cycles/min and centrifuged for 5 min at 750 $\times$ *g*. The methylene chloride phases were separated and evaporated to dryness. The residues were dissolved in 0.5 mL methanol. This process was completed within 3 h after phlebotomy. Then, 20-μL samples were injected into the chromatograph. The mobile phase of methanol-1% acetic acid (60:40 vol/vol) was pumped at 2.0 mL/min (about 2000 psi) using a solvent delivery system and pressure monitor (Rainin Instrument Co, Inc., Emeryville, CA, model: Rabbit-HP) through a stainless steel column (30 cm $\times$ 4 mm id) packed with a high-efficiency, reversed-phase packing (μBondapak C_{18}, P/N 27324, Waters Associates, Milford, MA). Ultraviolet absorbance was measured at 300 nm by using a V^4 absorbance detector (Isco Instrumentation Special Co., Lincoln, NE). Salsalate or salicylate concentrations were determined from the ratios of the salsalate or salicylate peaks to the α-phenylcinnamic acid peaks.

Data analysis and statistics

All sera from a single individual were assayed in a single assay run for each analyte. Individual values are the mean of three determinations (except for TrT_3, which was the mean of duplicates). Group means are the means of individual values. Repeated-measures ANOVA was used to test the statistical significance of the differences between each time point after salsalate ingestion, as compared with basal (zero-time).

Considering that the potency of salsalate for the inhibition of T_4 binding to serum proteins is 100-fold greater than that of salicylate (16), salicylate concentrations were divided by 100 to provide salicylate relative inhibitory potential, then added to salsalate concentrations to provide a measure of combined inhibitory potential (Table 1).

Results

Mean salsalate concentrations reached a peak of 82 μg/mL (0.320 mmol/L) at 2 h after salsalate ingestion, fell to 1.2 μg/mL (0.005 mmol/L) at 8 h, and became undetectable thereafter. Mean salicylate concentrations reached a peak of 211 μg/mL (1.318 mmol/L) at 4 h, fell to 11 μg/mL (0.066 mmol/L) at 48 h, and were undetectable thereafter (Table 1). The combined inhibitory potential reached a maximum at 2 h, of which salsalate accounted for 97%. The combined inhibitory potential at 4 h was 80% of maximum (salsalate accounting for 95%), then fell to 5% and 3% of maximum at 8 h and 24 h, respectively (Table 1). It is reasonable to conclude, therefore, that salsalate *per se* was the agent primarily responsible for inhibiting T_4 and T_3 binding and that the salicylate (produced by biotransformation of salsalate) contributed little. Serum TBG, transthyretin, and albumin concentrations were unchanged throughout the study. Mean TBG concentrations throughout were 2.23 mg/dL, mean transthyretin concentrations were 25.27 mg/dL, and mean albumin concentrations were 4.59 g/dL.

TABLE 1. Salsalate and salicylate concentrations (mean ± SE) after salsalate ingestion and their inhibitory potentials

Time (h)	Salsalate (mmol/L)	Salicylate (mmol/L)	Salicylate relative inhibitory potential[a]	Combined inhibitory potential[a]
0	0.000 ± 0.000	0.000 ± 0.000	0	0
2	0.320 ± 0.054	1.058 ± 0.187	0.011	0.331
4	0.252 ± 0.025	1.318 ± 0.111	0.013	0.265
8	0.005 ± 0.003	1.109 ± 0.092	0.011	0.016
24	0.000 ± 0.000	0.910 ± 0.126	0.009	0.009
48	0.000 ± 0.000	0.066 ± 0.030	0.0007	0.0007

[a] Taking into account the 100-fold greater inhibitory potency of salsalate as compared with salicylate (Ref. 16).

Serum TT_3 and TT_4 concentrations declined after salsalate ingestion, as expected. Both reached nadir values at 4 h, and both returned to basal levels by 96 h (Fig. 1A). However, their patterns of decline and recovery were different. TT_3 showed the greater decline, falling to 45% of basal, whereas TT_4 fell to 60% of basal. At 8 h, TT_3 had risen to 51% of basal and TT_4 to 77% of basal (Fig. 1A). Serum TrT_3 concentration declined to 23.2 ng/dL (81% of basal) at 2 h after salsalate ingestion, compared with the basal value of 28.7 ng/dL, then it rose above the basal value to 33.6 ng/dL (117% of basal) at 8 h ($P < 0.001$) (Fig. 1A). It returned to basal level by 24 h, remaining at basal concentrations thereafter. The ratios of TT_3 to TT_4 and TrT_3 to TT_4 were compared in Fig. 1B. The ratio of TT_3 to TT_4 declined after salsalate ingestion and reached its nadir at 8 h, whereas the ratio of TrT_3 to TT_4 increased and reached its peak at 8 h. The former returned to basal by 72 h, and the latter returned to basal by 24 h.

With the free hormone methods used, we could not demonstrate the expected early increase in FT_4 or FT_3 concentrations after inhibition of T_4 and T_3 binding to transport proteins. Because free hormone measurements were obtained by equilibrium dialysis, which imposes dilution upon the small (dialyzable) molecules in serum (including salsalate and salicylate), measurements during the time when salsalate or salicylate was present in sera at inhibiting concentrations (*i.e.* up to 24 h, Table 1) are likely underestimates of actual free hormone concentrations (17). For this reason, the FT_4 and FT_3 data during the first 24 h after salsalate administration were deleted from analysis (the deleted FT_4 measurements were 1.29 ng/dL at 2 h and 1.05 ng/dL at 4 h, 1.32 ng/dL at 8 h, and 1.44 ng/dL at 24 h, compared with the basal value of 1.52 ng/dL; the corresponding FT_3 measurements were 204 pg/dL at 2 h and 172 pg/dL at 4 h, 187 pg/dL at 8 h, and 247 pg/dL at 24 h, compared with the basal value of 358 pg/dL). The ratios of FT_3 to FT_4 were similar to those of TT_3 to TT_4.

The status of T_4 and T_3 binding to carrier proteins is shown in Fig. 1, D and E. Fig. 1D compares the time courses of TT_4 concentrations with FT_4 concentrations, represented as percentages of basal values. TT_4 showed the greater reduction and slower recovery, not returning to basal levels until 96 h. FT_4 did return to basal levels at 48 h. TT_4 was reduced, relative to FT_4, at 48 h, suggesting reduced binding to transport proteins at a time when salsalate and salicylate were undetectable. The time courses of TT_3 and FT_3 are compared in Fig. 1E. The decline and recovery patterns of the two were similar, providing no evidence of decreased T_3 binding during recovery. As a measure of T_4 to T_3 conversion, FT_3 was compared with FT_4 in Fig. 1C. The pattern of FT_3 recovery was different from that of FT_4 recovery. FT_4 recovered within 24 h, whereas FT_3 did not recover until 96 h. FT_3 was reduced, compared with FT_4, between 48 h and 72 h.

Serum TSH concentrations fell to a nadir at 8 h, which was 41% of basal value (Fig. 1F). This was 4 h after the nadirs of TT_4 and TT_3 and coincident with the nadir of the TT_3/TT_4

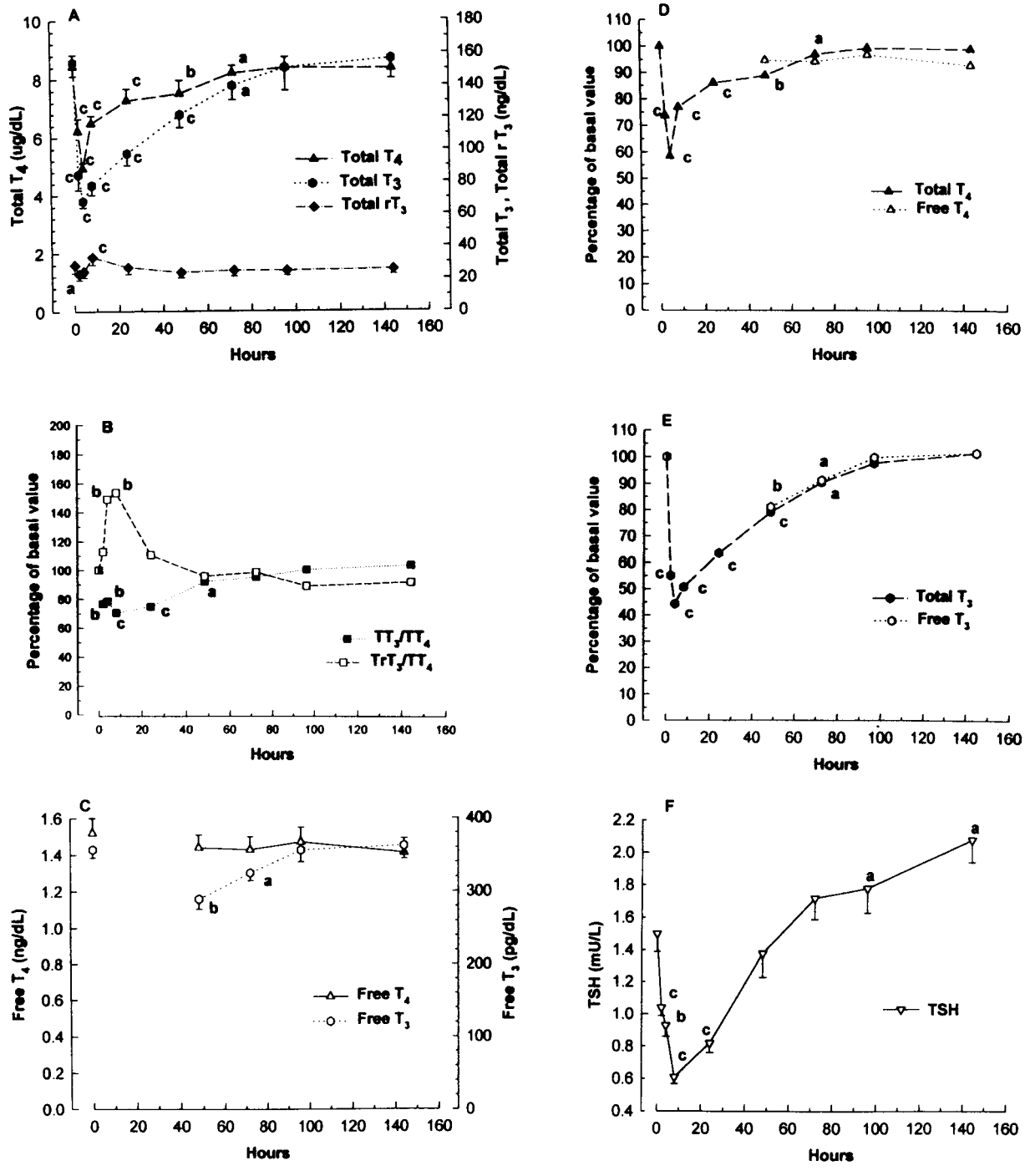

FIG. 1. A, TT_4, TT_3, and TrT_3 concentrations after salsalate ingestion (means and SE); B, comparison of the ratios of TT_3/TT_4 and TrT_3/TT_4, when expressed as percentages of basal concentrations, to assess changes in peripheral conversion of T_4 to T_3 and of rT_3 to T_2; C, FT_4 and FT_3 measurements after salsalate ingestion, to assess free T_3/free T_4 ratio (the 2-, 4-, 8-, and 24-h data were deleted, see *Results*); D and E, comparisons of total with free thyroid hormone concentrations, when expressed as percentages of basal concentrations, to assess changes in thyroid hormone binding; F, TSH concentrations after salsalate ingestion. TSH was significantly reduced between 2 h and 24 h, then significantly elevated from 96 h onward. Statistical significance was represented by: a, $P < 0.05$; b, $P < 0.01$; and c, $P < 0.001$.

ratio and the peak of the TrT_3/TT_4 ratio (Fig. 1B). TSH returned to basal level by 48 h, at a time when TT_4, TT_3, and FT_3 (but not FT_4) were still reduced. TSH then rebounded to levels above basal levels at 96 h and continued to rise for the duration of the study (6 days), whereas all thyroid hormones remained at basal levels (Fig. 1F).

Discussion

The timing of the rise and fall of serum salsalate and salicylate concentrations was similar in the present study (Table 1) to data previously reported by Harrison *et al.* (9). The salsalate peak of 82 μg/mL (0.32 mmol/L) was below its

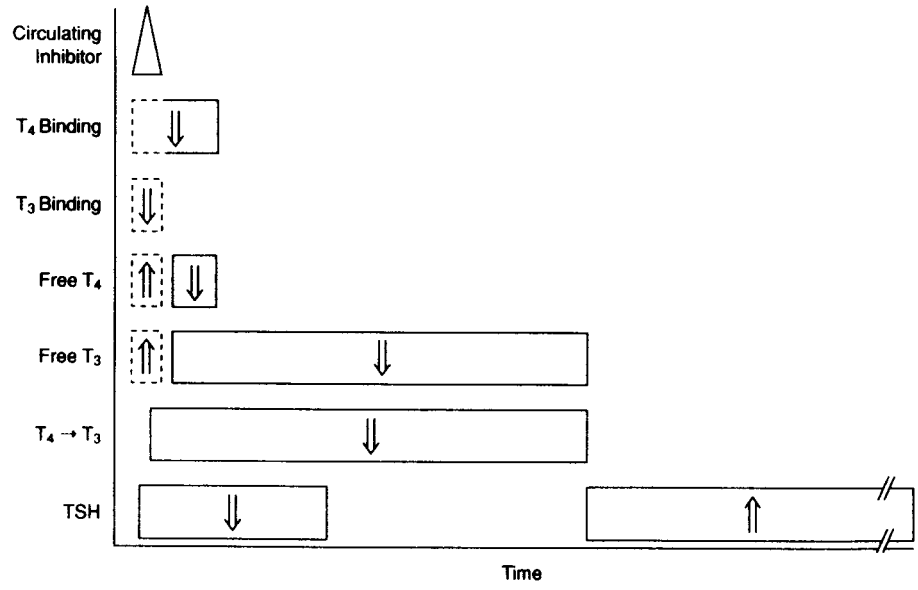

FIG. 2. Cartoon summarizing the observed (*solid lines*) and postulated (*broken lines*) changes induced by an oral dose of an inhibitor of T_4 and T_3 binding to serum proteins (salsalate). With the appearance in the circulation of inhibitor, T_4 and T_3 binding were reduced (and transient elevations of FT_4 and FT_3 are postulated). Concurrently, peripheral T_4-to-T_3 conversion and serum TSH concentrations declined, and they remained low after disappearance of inhibitor from the circulation. Low serum FT_3 with normal FT_4 was at first associated with reduced serum TSH, then with normal serum TSH. Later, after all thyroid hormone concentrations returned to basal, serum TSH concentrations were elevated.

therapeutic range of 100–300 μg/mL (0.39–1.16 mmol/L; see Ref. 18) and the salicylate peak of 211 μg/mL (1.32 mmol/L) was within its therapeutic range of 120–350 μg/mL (0.75–2.19 mmol/L; see Ref. 19). In a separate study, the potency of salsalate in displacing T_4 from serum transport proteins was approximately 100-fold greater than that of salicylate (16). Similar data have been reported by Bishnoi *et al.* (7).

The hormone changes, after binding inhibition, were complex (Figs. 1, A–F). TT_4 and TT_3 concentrations both declined, as expected, with TT_3 demonstrating a proportionately greater decline (Fig. 1A). The simplest explanation for the observed fall in TT_4 and TT_3 concentrations is an acute release of T_4 and T_3 from their serum transport proteins, resulting in rapid, transient elevations of circulating free hormone levels associated with redistribution of these hormones from the circulation into tissue compartments. The decline in total thyroid hormone concentrations could not be attributed to reductions in carrier protein concentrations, because these protein concentrations did not change. Neither can it be attributed to drug-induced primary hypothyroidism, because TSH did not rise (Fig. 1F).

FT_4 returned to basal levels at 48 h, whereas TT_4 did not return to basal levels until 96 h (Fig. 1D). The reduction of TT_4, relative to FT_4, at 48 h suggests a decrease of T_4 binding to carrier proteins at a time when circulating salsalate and salicylate levels were negligible (Table 1, Fig. 1D). The reason(s) for this finding is unclear. Because TT_3 and FT_3 recovered in parallel (Fig. 1E), the low TT_3 concentration during recovery can be attributed to the low FT_3 concentration (the T_3 available for binding), rather than reduced protein binding. In theory, the low FT_3 might be caused by reduced peripheral conversion of T_4 to T_3 or to a slow reentry of T_3 into the circulation from tissue, as compared with the reentry of T_4. The ratios of TT_3 to TT_4 and TrT_3 to TT_4 may represent the peripheral conversion of T_4 to T_3 and rT_3 to 3,3′-diiodothyronine (T_2), respectively. The decreased ratio of TT_3 to TT_4 plus the increased ratio of TrT_3 to TT_4 suggest the conclusion that there was a transient reduction in peripheral tissue 5′-monodeiodination (Fig. 1B).

The declines in circulating TT_4 (40% disappearance in 4 h) and TT_3 (55% in 4 h) after salsalate ingestion were many folds more rapid than the reported hormone half-lives in healthy adults with normal transport proteins (6–8 days for TT_4 and 1 day for TT_3) (20). This rate of decline is best explained by reduced hormone binding and a rapid redistribution of T_4 and T_3 from the circulation into tissue compartments. In healthy adults, the mass of circulating T_4 is approximately 450 μg. The tissue T_4 pool is also 450 μg. Consequently, the extrathyroidal T_4 pool is 900 μg (21). The mass of circulating T_3 is 6 μg, and that of tissue T_3 is 34 μg, with a extrathyroidal T_3 pool of 40 μg (21). Because TT_4 was reduced 40% and TT_3 was reduced 55%, it could be calculated that approximately 200 μg T_4 and 3.3 μg T_3 moved from the circulation into tissues within 4 h. The amount of T_4 transferred was large, relative to the amount of T_3 transferred, even after correcting for a 4-fold greater biological potency of T_3. Based on this, we conclude that T_4 was the primary effector of the TSH changes observed in this study. Raising the levels of T_4 (and T_3) in pituitary thyrotrophs and hypothalamic TRH-secreting neurons would be expected to suppress TSH secretion (22). Raising levels of T_4, and perhaps T_3, in rapidly equilibrating tissues (liver and kidney) may reduce 5′-monodeiodinase activity.

Spencer *et al.* reported serum TSH suppression after single or multiple doses of thyroid hormones (23). They showed that the rate of TSH decline was largely independent of, whereas the duration of TSH suppression was directly dependent upon, dosage. In that study, the half-life of disappearance of TSH from the circulation was approximately 6 h, which is similar to the 59% decline of TSH at 8 h in the present study.

The recovery of serum total thyroid hormone concentrations can be attributed, in part, to restored thyroid hormone binding to transport proteins, with a subsequent return of thyroid hormones from peripheral tissue compartments into the circulation. It cannot be attributed to increased TSH stimulation of thyroid hormone secretion because TSH was at or below basal levels during T_4 and T_3 recovery.

There was an apparent biphasic derangement in the rela-

tionship of serum TSH to thyroid hormone concentrations after salsalate ingestion. At 4 h, TSH was suppressed at a time when total thyroid hormone levels were reduced (Fig. 1, A and F). From 96 h onward, TSH was elevated at a time when total and free T_4 and T_3 were at basal levels. This TSH elevation may be attributable to the prior exit of thyroid hormones from tissue compartments as binding to serum proteins recovered. The progressive increase in TSH levels from 96 h onward occurred without a detectable response of total or free T_4 or T_3. This may be attributable to one or both of two possible mechanisms: 1) disturbances in the circadian rhythm of TSH secretion without changes in the mean 24-h TSH concentrations (24, 25); and 2) reduced bioactivity of TSH, caused by reduced TSH glycosylation (26, 27).

Faber *et al.* studied the sequelae of a single oral dose of salicylate (1.5 g) and reported reduced TSH levels and increased FT_4 levels, as measured by both ultrafiltration and equilibrium dialysis, with a greater increase as determined by ultrafiltration, compared with dialysis (17). There are three points of comparison with our study: 1) In Faber's study, salicylate concentrations peaked at 0.7 mmol/L. In our study, salsalate peaked at 0.32 mmol/L. Both peaked at 2 h. 2) Faber reported a rapid increase in serum-free T_4 levels, by equilibrium dialysis, which we did not detect. 3) They observe a nadir in serum TSH that was 80% of basal value at 2 h. We observed a TSH nadir of 41% of basal value at 8 h. The greater inhibitory potency of salsalate may be one reason we observed reduced free T_4 values and Faber observed increased free T_4 values using the same equilibrium dialysis free T_4 method (see *Results*).

Chopra *et al.* reported that salicylate decreases the activity of rat hepatic 5′-monodeiodinase (28). In unpublished data, Chopra has also observed salsalate inhibition of rat 5′-monodeiodinase (personal communication). This may have contributed to reduced T_3 formation and impaired rT_3 degradation after salsalate ingestion in the present study.

Figure 2 is a cartoon summarizing the time course of the complex inhibitor-induced hormone changes observed in the present study. At different time periods, the various patterns of abnormal hormone relationships were similar to those reported in the sick euthyroid syndrome (29–31), indicating that inhibitor-induced compartmental shifts in T_3 and T_4 could be important mechanisms in the genesis of the complex thyroid hormone disorders associated with acute nonthyroidal illness, and that administration of thyroid hormone-binding inhibitors may provide useful pharmacologic models for studies of these changes.

The data raise two unanswered questions. First, what role, if any, do large and transient increases in tissue levels of T_4 and T_3 play in the decrease of T_4-to-T_3 conversion? Second, is there a direct suppression of TSH secretion by salsalate? Resolution of these questions must await further studies.

References

1. **Utiger RD.** 1995 The thyroid: physiology, thyrotoxicosis, hypothyroidism, and the painful thyroid. In: Felig P, Baxter JD, Frohman LA, eds. Endocrinology and metabolism. 3rd ed. New York: McGraw-Hill Inc; 435–519.
2. **Kaptein EM, Robinson WJ, Grieb DA, Nicoloff JT.** 1982 Peripheral serum thyroxine, triiodothyronine and reverse triiodothyronine kinetics in the low thyroxine state of acute nonthyroidal illnesses. J Clin Invest. 69:526–535.
3. **Chopra IJ, Chopra U, Smith SR, Reza M, Solomon DH.** 1975 Reciprocal changes in serum concentrations of 3, 3′, 5′-triiodothyronine (reverse T_3) and 3, 3′, 5-triiodothyronine (T_3) in systemic illnesses. J Clin Endocrinol Metab. 41:1043–1049.
4. **Wilcox RB, Nelson JC, Tomei RT.** 1994 Heterogeneity in affinities of serum proteins for thyroxine among patients with nonthyroidal illness as indicated by the serum free thyroxine response to serum dilution. Eur J Endocrinol. 131:9–13.
5. **Green WL.** 1991 Effect of drugs on thyroid hormone metabolism. In: Wu S-Y, ed. Current issues in endocrinology and metabolism: thyroid hormone metabolism–regulation and clinical implications. Boston: Blackwell Scientific; 239.
6. **Lim CF, Bai Y, Topliss DJ, Barlow JW, Stockigt JR.** 1988 Drug and fatty acid effects on serum thyroid hormone binding. J Clin Endocrinol Metab. 67:682–688.
7. **Bishnoi A, Carlson HE, Gruber BL, Kaufman LD, Bock JL, Lidonnici K.** 1994 Effects of commonly prescribed nonsteroidal anti-inflammatory drugs on thyroid hormone measurements. Am J Med. 96:235–238.
8. **Larsen PR.** 1972 Salicylate-induced increases in free triiodothyronine in human serum. Evidence of inhibition of triiodothyronine binding to thyroxine - binding globulin and thyroxine - binding prealbumin. J Clin Invest. 51(5):1125–1134.
9. **Harrison LI, Funk ML, Re ON, Ober RE.** 1981 Absorption, biotransformation, and pharmacokinetics of salicylsalicylic acid in humans. J Clin Pharmacol. 21:401–404.
10. **Harrison LI, Funk ML, Ober RE.** 1980 High-pressure liquid chromatographic determination of salicylsalicylic acid, aspirin, and salicylic acid in human plasma and urine. J Pharm Sci. 69:1268–1271.
11. **McConnell RJ.** 1992 Abnormal thyroid function test results in patients taking salsalate. JAMA. 267:1242–1243.
12. **Kabadi UM, Danielson S.** 1987 Misleading thyroid function tests and several homeostatic abnormalities induced by "Disalcid" therapy. J Am Geriatr Soc. 35:255–257.
13. **McConnell RJ.** 1989 Salsalate alters thyroid function test results. Arthritis Rheum. 32:1344.
14. **Latham BB, Horst E, Nankin H, Lin T, Osterman J.** 1993 Case report: abnormal thyroid function tests in a patient and two normal volunteers treated with salsalate. Am J Med Sci. 305:111–113.
15. **Visser TJ, Docter R, Hennemann G.** 1977 Radioimmunoassay of reverse tri-iodothyronine. J Endocrinol. 73:395–396.
16. **Wang R, Nelson JC, Wilcox RB.** "[^{14}C]-Salsalate binding to, and salsalate displacement of [^{125}I]-thyroxine (T_4) from, whole serum, thyroxine binding globulin (TBG), transthyretin and albumin". Proc of the 70th Annual Meeting of The American Thyroid Association, Colorado Springs, Colorado, 1997, S-87 (Abstract).
17. **Faber J, Waetjen I, Seirsbaek-Nielsen K.** 1993 Free thyroxine measured in undiluted serum by dialysis and ultrafiltration: effects of non-thyroidal illness, and an acute load of salicylate or heparin. Clin Chim Acta. 223:159–167.
18. 1998 Physicians' desk reference. 52nd ed. Montvale, NJ: Medical Economics Company, Inc; 1525–1526.
19. **Insel PA.** 1990 Analgesic-antipyretics and antiinflammatory agents; drugs employed in the treatment of rheumatoid arthritis and gout. In: Gilman AG, Rall TW, Nies AS, Taylor P, eds. Goodman and Gilman's the pharmacological basis of therapeutics. 8th ed. New York: Pergamon Press; 647.
20. **Greenspan FS, Rapoport B.** 1991 Thyroid gland. In: Greenspan FS, ed. Basic and clinical endocrinology. 3rd ed. East Norwalk, CT: Appleton & Lange; 205.
21. **Nicoloff JT, Ingbar SH, Braverman LE.** 1986 Werner's the thyroid a fundamental and clinical text. Philadelphia: J. B. Lippincott Company; 128–135.
22. **Abend SL, Fang SL, Alex S, Braverman LE, Leonard JL.** 1991 Rapid alteration in circulating free thyroxine modulates pituitary type II 5′ deiodinase and basal thyrotropin secretion in the rat. J Clin Invest. 88:898–903.
23. **Spencer CA, LoPresti JS, Nicoloff JT, Dlott R.** 1995 Multiphasic thyrotropin responses to thyroid hormone administration in man. J Clin Endocrinol Metab. 80:854–859.
24. **Romijn JA, Wiersinga WM.** 1990 Decreased nocturnal surge of thyrotropin in nonthyroidal illness. J Clin Endocrinol Metab. 70:35–42.
25. **Arem R, Deppe S.** 1990 Fatal nonthyroidal illness may impair nocturnal thyrotropin levels. Am J Med. 88:258–262.
26. **Magner J, Roy P, Fainter L, Barnard V, Fletcher Jr P.** 1997 Transiently decreased sialylation of thyrotropin (TSH) in a patient with the euthyroid sick syndrome. Thyroid. 7:55–61.
27. **Lee HL, Suhl J, Pekary AE, Hershman JM.** 1987 Secretion of thyrotropin with reduced concanavalin-A-binding activity in patients with severe nonthyroidal illness. J Clin Endocrinol Metab. 65:942–948.
28. **Chopra IJ, Solomon DH, Chua Teco GN, Nguyen AH.** 1980 Inhibition of hepatic outer ring monodeiodination of thyroxine and 3, 3′, 5′-triiodothyronine by sodium salicylate. Endocrinology. 106:1728–1734.
29. **Chopra IJ.** 1996 Nonthyroidal illness syndrome or euthyroid sick syndrome? Endocrine Practice. 2:45–52.
30. **Kaptein EM.** 1991 The effects of systemic illness on thyroid hormone metabolism. In: Wu SY, ed. Current issues in endocrinology and metabolism: thyroid hormone metabolism–regulation and clinical implications. Boston: Blackwell Scientific; 211.
31. **Tibaldi JM, Surks MI.** 1985 Effects of nonthyroidal illness on thyroid function. Med Clin North Am. 69:899–909.