Kinetics of the Human Thyroid Trap: Effects of Iodide, Thyrotropin, and Propylthiouracil

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Effects on the thyroidal pertechnetate trap of iodide, thyrotropin (TSH), and propylthiouracil (PTU), compared with duplicated control studies, were assessed in normal subjects using i.v. [Tc^{99m}] pertechnetate, a multicrystal scintillation camera, and a compartmental model.

Sodium iodide (1 g), administered orally on two occasions, 2 wk apart, caused an early drop in plasma clearance into the follicular cell ($p < 0.05$), with later return to normal clearance 1 wk after the second NaI dose. In this later study, exit from the colloid was elevated ($p < 0.01$). Plasma equivalent volume of the "colloid" compartment was reduced in both postiodine studies ($p < 0.05$).

Thyrotropin, 10 units intramuscularly, was followed by no significant changes in trap parameters at 2 hr. At 24 hr, plasma clearance had doubled ($p < 0.05$), and the plasma equivalent "colloid" volume had tripled ($p < 0.01$).

Propylthiouracil was given as a single 1 g dose 1 hr before a trapping study, followed by 200 mg PTU every 8 hr for 1 wk. The first dose resulted in apparent reduction in all of the rate constants for transport across the basal and apical thyroid follicular cell membranes; these rates returned toward control levels after 1 wk. The plasma equivalent "follicular cell" volume was reduced to 66% of control levels ($p < 0.025$) after 1 wk PTU. These effects must be taken into account in the interpretation of studies of the trap based on PTU pretreatment to inhibit organification.

J Nucl Med 20: 944–949, 1979

When thyroid function is normal, direct study of the thyroidal iodide-concentrating mechanism (the "trap") is complicated by the presence of organically bound iodine within the thyroidal follicular cell and colloid. Chemical methods to separate iodide from organically bound iodine are not applicable to the intact human subject. Even when feasible in experimental situations, chemical methods may be complicated by release of iodide from the protein-iodine complexes. Prevention of organification of intrathyroidal iodine by use of antithyroid drugs has proven a useful technique for study of the trap (*1*). However, the possibility that the antithyroid drugs themselves affect the trap needs to be explored.

Pertechnetate is trapped by the thyroid much as iodide is, but does not enter into quantitatively significant binding to thyroglobulin in the normal human thyroid (*2*). Its thyroidal transport is competitively inhibited immediately after iodide administration in vitro (*1*) and in vivo (*3*). Hence it appears to provide a good model for the thyroidal iodide trap.

Received Dec. 19, 1979; revision accepted April 2, 1979.

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We have previously reported development of a compartmental model for the thyroid trap, demonstrating the presence of two thyroidal compartments, presumed to represent the follicular cell and the colloid (*3*). Experience from applying this analytic technique to pertechnetate uptake data in a variety of control situations has also been reported (*4*), together with results in a small series of patients with thyroid disease.

In the present report, the delayed effects of iodide, the early and intermediate effects of thyrotropin (TSH), and the early and delayed effects of propylthiouracil (PTU) on the normal human thyroid trap were assessed, using thyroidal pertechnetate transport as the experimental model for the trap. Evidence is presented that all of these agents affect the trap, at least after administration to normal young human subjects in an experimental situation.

METHODS

Seventeen paid volunteers—12 men and 5 women, aged 21 to 29 yr—were subjects of these studies. All were euthyroid clinically and chemically. Subjects gave written informed consent before initiation of the study, which was approved by an institutional human research committee.

[^{99m}Tc]pertechnetate thyroidal concentration studies were performed using a multicrystal scintillation camera, with specific identification of counts in the areas of the thyroid and the neck background. Data were collected continuously for 40 min after a 2-mCi i.v. dose of pertechnetate. Plasma radioactivity was measured in samples obtained at 2, 5, 10, 20, 30, and 40 min. These data were analyzed by use of a mathematical model (Figs. 1-3) fitted using the SAAM compartmental modeling technique (*5*) and a digital computer. The detailed protocol of the test and the details of method and of the model development have been reported earlier (*3*).

Before receiving the experimental agents, each subject underwent two (n = 14) or three (n = 3) control studies. Geometric means of the parameters from these studies were used as the control values for assessment of experimental results.

Accidental magnetic-tape erasure destroyed the data from three individual session studies. These were dealt with in the following ways.

1. When one of two control studies was lost (one subject), parameters from the single remaining control study of this subject were used instead of the geometric mean.
2. When one 2-hr post-TSH study (a male subject) and one 24-hr post-TSH study (a female subject) were lost, these were omitted from statistical analyses of paired data and of the respective experimental periods. However, the means for the experimental periods in Table 2 include their interpolated values.

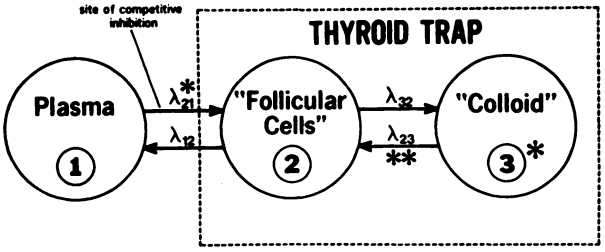

FIG. 1 Three-compartment model of thyroidal trap, illustrating sites of iodide effect. * Reduced ($p < 0.05$); ** Increased ($p < 0.01$).

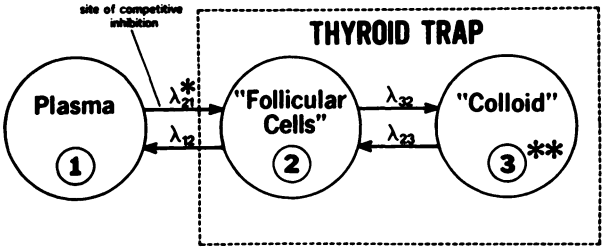

FIG. 2. Model illustrating sites of TSH effect. * Increased ($p < 0.05$); ** Increased ($p = 0.02$).

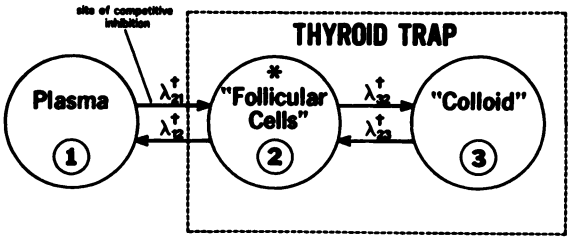

FIG. 3. Model illustrating sites of PTU effect. † Reduced (see caption of Table 3); * Reduced ($p < 0.05$).

In all studies, the control sessions were completed before administering the experimental substance (iodide, TSH, or PTU).

Iodide experiment (three men, three women). Subjects received two doses of 1000 mg NaI orally, spaced 2 wk apart. Trapping studies reported here were initiated 1 wk after the first dose, and 1 wk after the second dose (3 wk after the first dose). The final study was not done on one female subject. In the final study, an oral dose of 1000 mg $KClO_4$ was administered at the midpoint (after 20 min of

data collection). Data from this final session were analyzed by setting λ_{21} to zero at the experimental change-point as reported previously (*3*). In the earlier study, both iodide and $KClO_4$, when given at the midpoint of the trapping study, caused abrupt cessation of transport across the basal membrane (λ_{21}) but fit remained good if other parameters remained unchanged. In the present study, it is assumed that, with this adjustment to correct for the acute competitive inhibition of unilateral clearance, parameters in the final study can be compared freely with those of studies not interrupted by a midpoint blockade. This assumption is based on the analogy of perchlorate blockade to iodide blockade and to the following facts: a) good fits were obtained for the entire curve, whether the acute block was with iodide or perchlorate; and b) in the case of mid-study iodide blockade, no previous iodide had been administered. Under these circumstances, the parameters of fit did not differ from those of the control studies (Ref. *3* and Table 1 of this paper).

TSH experiment (five men, one woman). Each subject received a single dose of 10 units commerical bovine TSH intramuscularly. Trapping studies were initiated 2 hr, and again 24 hr, after TSH administration.

PTU experiment (four men, one woman). Each subject received a single oral dose of PTU, 1000 mg, given at least 2 hr after breakfast. A trapping study was initiated 1 hr later. For the following week, the subject continued to take PTU, 200 mg every 8 hr. At the end of this week of PTU administration, another trapping study was performed.

TABLE 2. TSH STUDY. EFFECTS OF PRIOR TSH ADMINISTRATION ON THYROIDAL TRAP PARAMETERS*

Plasma equivalent volume (ml)	Control	2 hr after TSH	24 hr after TSH
V_2	15 (3–32)	21 (10–45)	38 (18–82)
V_3	59 (27–269)	55 (13–164)	187† (94–266)
Rate constants			
λ_{21} (ml/min)	4.1 (2.3–7.4)	4.4 (2.0–8.2)	10.7‡ (8.6–12.0)
λ_{23} (ml/min)	0.070 (0.027–0.128)	0.082 (0.050–0.156)	0.057 (0.042–0.111)
$\lambda_{12} = \lambda_{32}$ (ml/min)	0.28 (0.13–0.88)	0.09 (0.01–0.20)	0.12 (0.02–0.53)

* Geometric means with range in parentheses.
† Differs from control ($p = 0.02$).
‡ Differs from control ($p < 0.05$).

RESULTS

Parameters were analyzed in logarithmic form, using geometric means, since analysis of a large control series (*4*) has shown the distribution to be more nearly log-normal than normal. There is considerable individual variability in the control parameters of the subjects, as shown by the wide ranges in Tables 1 through 3. Standard deviations are comparable to those observed in the larger control series.

Iodide experiment. Delayed effects of iodide on

TABLE 1. IODIDE STUDY. EFFECTS OF PRIOR IODIDE ADMINISTRATION ON THYROIDAL TRAP PARAMETERS*

Plasma equivalent volume (ml)	Control	Control (iodide 1 g at mid point)†	1 wk after 1 g NaI	3 wk after 1st dose NaI; 1 wk after 2nd dose 1 g NaI. ($KClO_4$: 1 g at mid point)†
V_2	14 (7–30)	18 (11–39)	12 (2–23)	14 (4–47)
V_3	112 (49–350)	113 (38–452)	60‡ (15–317)	51‡ (14–211)
Rate constants				
λ_{21} (ml/min)	4.5 (2.5–7.5)	4.0 (1.4–11.0)	2.9* (1.4–5.8)	4.3 (1.6–10.6)
λ_{23} (ml/min)	0.041 (0.016–0.102)	0.036 (0.020–0.089)	0.049 (0.018–0.094)	0.088‖ (0.050–0.155)
$\lambda_{12} = \lambda_{32}$ (ml/min)	0.31 (0.13–0.76)	0.23 (0.08–0.51)	0.24 (0.10–0.44)	0.31 (0.22–0.51)

* Geometric means with range in parentheses.
† When NaI or $KClO_4$ was given at mid point of study, λ_{21} was reset to zero in model fit at time when blocking agent effect began to be seen (at 20 min after i.v. NaI, at individualized times for oral dosage (*1*)). Except for this change, fit in these studies incorporates all parameters and all data.
‡ Differs from control ($p < 0.05$).
‖ Differs from control ($p < 0.01$).

TABLE 3. PTU STUDY. EFFECTS OF PRIOR PTU ADMINISTRATION ON THYROIDAL TRAP PARAMETERS*

Plasma equivalent volume (ml)	Control	PTU 1000 mg 1 hr before	PTU 200 mg q 8 hr for 1 wk
V_2	23 (16–37)	21 (7–55)	15† (7–26)
V_3	90 (19–205)	87 (11–308)	77 (11–205)
Rate constants			
λ_{21} (ml/min)	4.9 (2.0–10.0)	2.7‡ (1.1–12.9)	3.5 (0.7–9.6)
λ_{23} (ml/min)	0.056 (0.028–0.109)	0.028‡ (0.011–0.097)	0.045 (0.009–0.111)
$\lambda_{12} = \lambda_{32}$ (ml/min)	0.25 (0.12–0.37)	0.12‡ (0.03–0.27)	0.24 (0.01–0.64)

* Geometric means with range in parentheses.
† Significantly different from control ($p < 0.05$).
‡ When data on three rate constants, λ_{21}, λ_{23}, and ($\lambda_{12} = \lambda_{32}$), are combined, each individual datum being compared with its corresponding control value, decrease is significant at $p = 0.002$. Taken separately, for λ_{21}, $p = 0.145$; for λ_{23}, $p = 0.053$; and for ($\lambda_{12} = \lambda_{32}$), $p = 0.141$.

the trap parameters are presented in Table 1 and illustrated in Fig. 1. One week after a single massive dose of 1000 mg NaI, the clearance into the trap (λ_{21}) was reduced by 32% ($p = 0.033$ for matched pairs), and the plasma equivalent volume of "colloid", V_3, was reduced by 46% ($p = 0.024$). At one week the apparent 27% increase in the exit rate from the colloid, λ_{23}, was not statistically significant ($p = 0.342$). Two weeks later, when a trapping study was performed 3 wk after the original dose of NaI and 1 wk after the second dose, the mean value of λ_{21}, the clearance, had returned to control values. However, V_3 was by then reduced to 45% of control levels ($p = 0.025$) and the exit constant, λ_{23}, had increased to 229% of control levels ($p = 0.004$).

Examination of data from individual subjects confirmed that V_3 had decreased in every case in both postiodide studies, and that in all but one case, V_3 was lower in the later study than in that at 1 wk. At 1 wk, λ_{21} was lower in four cases and unchanged in two; at 3 wk it remained low in two cases, but in two others it was increased above control levels, suggesting a "rebound" phenomenon. At 1 wk, λ_{23} was increased above control levels in four of six cases, with increases at 3 wk in all five of the subjects studied. Examination of individual patterns for the other parameters showed no consistent pattern.

TSH experiment. Effects of 10 U bovine TSH given 2 hr or 24 hr before the trapping study are presented in Table 2 and illustrated in Fig. 2. No significant changes were noted at 2 hr. In four of the five cases, V_2 was greater in the 2-hr study than in that subject's mean control, but these changes were small in magnitude.

At 24 hr, the clearance, λ_{21}, was 161% above control values ($p = 0.026$) and had increased in all cases. Four of five cases had increased V_3, and the mean V_3 was 217% above control ($p = 0.020$). In all five cases V_2 was increased, with a geometric mean increase of 153%. This change was quite variable and was not statistically significant by paired-t test ($p = 0.162$), though the nonparametric "sign" test was significant ($p = 0.031$).

The apparently lower mean values for ($\lambda_{12} = \lambda_{32}$) in the two experimental sessions were associated with marked individual variability and were not statistically significant ($p = 0.160$ at 2 hr and 0.685 at 24 hr).

Propylthiouracil experiment. Effects of PTU on the individual parameters are presented in Table 3 and Fig. 3.

One hour after the 1000-mg dose of PTU, the thyroidal exit rate constant, λ_{23}, slowed ($p = 0.053$) and the other rate constants appeared to slow [$p = 0.143$ for λ_{12}, and 0.145 for ($\lambda_{12} = \lambda_{32}$)]. When λ_{21}, λ_{23}, and ($\lambda_{21} = \lambda_{32}$) were pooled in analysis of paired studies, the overall slowing after the acute dose was highly significant ($p = 0.002$). After 1 wk of continued PTU intake, the rate constants all moved back toward control levels.

V_2 was unchanged after the acute dose of PTU, but decreased by 35% after 1 wk ($p = 0.023$).

Geometric mean V_3 appeared to be 15% below control after 1 wk of PTU, but this was not statistically significant ($p = 0.57$).

DISCUSSION

Interrelating effects of iodide and thyrotropin on the thyroidal trap, and the possible effect of the antithyroid drugs often used to study the trap, have made elucidation of the separate effects of these agents difficult. Nevertheless, it appears well established that iodide and thyrotropin influence the trap by independent mechanisms (*6–8*). Whether propylthiouracil has a primary effect on the trap is less well established.

In the present study, both clearance into the thyroid, λ_{21}, and the exit constant, λ_{23}, are affected after iodide administration, but the decrease in clearance predominates at 1 wk and the increase in exit constant predominates at 3 wk. V_3, calculated from the ratio of λ_{21} to λ_{23} (which roughly corresponds to T/S in animal studies) is decreased in both the 1- and the 3-wk studies. Hence, our data partially confirm both the published studies indi-

cating that increasing serum iodide reduces unidirectional clearance across the basal cell membrane (*9, 10*), and those suggesting that the primary influence is an increase in exit constant (*11*).

It is important to distinguish between the delayed effects of iodide studied here and the acute competitive inhibition of transport induced immediately after a bolus of iodide (*3*). The later effect has been shown to disappear, in the absence of organification of iodine, when cell preparations are washed free of excess iodide before a study (*6,7,12*). It may, however, be related to the acute decrease noted even in preparations leached of excess iodide in experiments where organification of the excess iodide is allowed (*6,7,12*).

It is quite possible that the delayed effects of the second iodide dose in our experiment differed qualitatively from those of the dose given 2 wk previously because of iodide "adaptation" to overcome the Wolff-Chaikoff effect (*7*). Enhancement of the exit constant is a possible mechanism for this adaptation. Whether the exit constant represents an "active" function—presumably transport across the apical follicular-cell membrane—is a point that has been debated (*10,13,14*). Acceptance of the apical as well as the basal cell membrane as a site for potential stimulation or inhibition implies the validity of models with two thyroid compartments (*3,15*). Increase in the exit constant has been reported in thiocyanate treatment (*13,14,16*), in increased dietary iodine (*11*), with increasing time of day (*4*), in remission after I-131 treatment of Graves' disease (*4*), and early after TSH (*8,17*).

One must use caution in assessing data from the final session of the iodide study, since subjects were given $KClO_4$ at the midpoint of the study. Midpoint administration of both iodide and $KClO_4$ were used in validations of the basic model (*3*). In our interpretation, we have assumed that this session was comparable to the session in which a large iodide dose was given at the midpoint. Fits appeared to be good, assuming that only λ_{21} was affected in either study. However, it is possible that the $KClO_4$ itself might have increased the exit constant by a mechanism not shared by iodide. Had that happened, the final fit would have been a compromise between the λ_{23} values before and after $KClO_4$. Such a shift was not apparent, but our method of analysis may not be sufficiently sensitive to detect a minor shift.

It has been amply demonstrated in the literature (e.g., *17*) that TSH stimulates the thyroid trap, but after a time delay. Early after TSH, suppression of uptake has also been shown to occur in man (*18*), in dogs (*8*), and in thyroid lobes in vitro (*17*). This early suppression is probably due to increased iodide efflux from the follicle, at least partially due to release of trapped iodide (*8,17*). It is unclear why no early suppression was observed in the present series. The single study of 2 hr may have missed a critical point on the time scale, though the decreased early radioiodide uptake after TSH in man was observed at 2 hr (*18*).

The parameter changes seen 24 hr after TSH parallel those seen in Graves' disease (*4*), although they are less marked quantitatively. The primary site of stimulation appears to be at the basal cell membrane, since λ_{21} was increased in all subjects. This increase in λ_{21} is primarily responsible for the major increase in V_3 in four subjects at 24 hr, although in three of these subjects the V_3 increase was accentuated by an associated decrease in λ_{23}. One subject had no change in V_3 24 hr after TSH. He had unusually high control V_3 levels, associated with unusually low control λ_{23}. Identification of the basal cell membrane as the primary site of delayed TSH effect on the thyroidal trap is compatible with the concept that, over a matter of hours after administration, TSH leads to an increase in the, as yet uncertain, energy-consuming process that facilitates ion transport into the follicular cell (e.g., *6, 19*).

The major effect of an acute dose of PTU on thyroidal pertechnetate transport appears to be an overall slowing, in both directions, of transport across the basal and apical follicular-cell membrane. By 1 wk after initiation of PTU, exit from the follicular cell has returned to control levels. Entry into the cell across the basal cell membrane (λ_{21}) and the apical cell membrane (λ_{23}) appear slightly reduced, but not significantly so. However, at 1 wk the plasma equivalent pertechnetate volume of the follicular cell, V_2, has become reduced. This reduction is small in magnitude and its implications are obscure. Alterations in V_2 in clinical studies (*4*) appeared to be associated with corresponding alterations in vascular and/or follicular-cell anatomic volume in the thyroid gland. It is possible that the decrease in V_2 seen after 1 wk of PTU reflects such an anatomic change.

Acute blockage of iodine organification by antithyroid drugs has been a useful tool in study of the thyroidal iodide-concentrating mechanism (*1,6,7,9–15,17*). The small effect of PTU demonstrated in this study probably would not invalidate the interpretation of such studies, when they measure qualitative effects. Nevertheless, the possibility of a relative PTU inhibition of iodide transport across the basal and/or apical thyroid follicular-cell membrane must be taken into account when such studies are interpreted.

It is unlikely that the effects of PTU on the trap make a significant contribution to the therapeutic

effect of the drug when it is used in patients with hyperthyroidism. It should be considered, however, when pertechnetate studies are used prognostically in such patients.

ACKNOWLEDGMENTS

The author thanks Mones Berman, National Cancer Institute, for his generous advice and instruction in use of the SAAM modeling technique, and for making the resources of his laboratory available. Dr. Robert McGuire provided important advice and assistance in the analysis of the data. Ms. Sarah Paul provided valuable technical assistance.

This study was supported by Veterans Administration Intramural R & D Funds.

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